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EXPERIMENTAL PELLAGRA IN WHITE MALE CONVICTS *

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WASHINGTON, D. C.

Four years ago we published a brief note [1] on a feeding experiment, carried out at the Mississippi State Penitentiary, in which we reported the successful production of pellagra in some white male convicts. Preparation of the detailed report of this experiment was unavoidably delayed by the pressure of continuing field investigations, but has now been completed and is in course of publication.[2] Because of the importance of some new points relating to the etiology of the disease that certain observations in connection with the experiment suggest, it has seemed worth while to present on this occasion a somewhat condensed report of this experiment and of the indications that it affords.

PURPOSE

The purpose of the experiment was to test the possibility of producing pellagra in previously healthy men by feeding a one-sided, monotonous, principally cereal diet of the type observed by us in other previous studies to be associated with a high incidence of the disease.

PLAN OF EXPERIMENT

The experiment was carried out at the Rankin farm of the Mississippi penitentiary. The subjects were white male convicts who volunteered for the purpose. White adult males were chosen in order to make the test as rigorous as possible, for, judging by the then available incidence data, this race, sex and age group seemed least susceptible to the disease.

Believing that the significance of the experiment would be enhanced if, in the event of success in producing pellagra, the attack or attacks

* From field investigations of Pellagra, U. S. Public Health Service.

* Read in the Section on Pathology and Physiology at the annual meeting of the American Medical Association, New Orleans, April 26-30, 1920.

1. Experimental Pellagra in the Human Subject Brought About by a Restricted Diet, Public Health Rep. **30**:3336 (Nov. 12) 1915; also: Pellagra; Causation and a Method of Prevention, J. A. M. A. **66**:471 (Feb. 12) 1916.

2. Bull. Hygienic Laboratory, No. 121.

developed at a season when the incidence and prevalence of the disease were normally on the decline, say in August or September, and having estimated that it would take about three or four months to develop the disease, it was planned to begin with the experimental diet early in May. As the organization of the volunteer squad was completed February 4, this provided a period of three months for preliminary observation. The growing impatience of the volunteers to begin and to get through with their ordeal obliged us, however, to begin the feeding about two weeks earlier than planned, namely, April 19, 1915.

During the preliminary period (February 4-April 19) the volunteers were provided the regular prison fare and were closely scrutinized for any evidence of pellagra that might already have existed. It also afforded time for them to become habituated to the desired routine of work and discipline.

As a condition of volunteering, it was agreed that the men would not be kept on the experimental diet longer than six months. They were freed and, with one exception, passed from observation Nov. 1, 1915. The period of the feeding experiment extended, therefore, from April 19 to and including Oct. 31, 1915, approximately six and one-half months.

CONTROLS AND SUBJECTS

The population of the farm is made up of the prison officials and their families and a fluctuating number of white male convicts.

Controls.—All persons other than the volunteers resident on the farm during the study were under observation as controls. This included a total of 108 convicts. Of these, thirty were present and under observation from the beginning to the end of the study; of five others, one was present at the beginning and continued under observation to October 26, while four were admitted in February, early during the preliminary observation period, and remained to the end. Practically, therefore, we had under observation a control group of thirty-five convicts for a period comparable to the period of observation of the subjects of the experiment. In age, the members of this control group varied between 19 and 51 years. All denied having had pellagra.

There were resident at the farm a varying number of free individuals (officers and their families) of whom twelve were present throughout the study. Included in this group were six adult males, four adult females and two children, one a boy 12 years of age, and the other a girl 2 years of age. This group is of special interest because of the supposed greater susceptibility of women and children. None of this group of free controls gave a history of pellagra.

Subjects.—The squad of twelve volunteers, or "pellagra squad," as it came to be called, was organized between February 1 and February 4,

segregated and placed under a special guard employed for that purpose and under our control. The ages of these men varied between 24 and 50 years. None gave a history of having had pellagra, or of the occurrence of the disease in any member of the family or a near relative.

July 1, one of this group was released because of the development of a condition thought to be a prostatitis. This left eleven men who remained in the test to its close.

GENERAL ENVIRONMENT

Farm.—The prison farm is located in Rankin County, about eight miles east of the City of Jackson, Mississippi. It is roughly a square of about 3,200 acres. The country surrounding the farm is sparsely settled.

Camp.—A little to the north of the center of this farm is located the group of prison, official residence and farm buildings locally designated as the "camp." Near the center of this camp is a fence-enclosed quadrangular area within which are the structures, "cage" etc., in which the general convict population was housed. The volunteers were lodged in the so-called new hospital, a small, one-story cottage, of recent construction, about 500 feet southeast of the "cage" and outside of the stockade. Originally intended for use as the camp hospital, this cottage had served instead as a tailor shop and as quarters for one of the trusties and one of the assistant wardens. By reason of this, the cottage was, by comparison with the quarters of the other convicts, exceptionally clean. In addition it was given a general overhauling and thorough cleaning before the volunteers were lodged therein.

Screening.—All of the residence buildings and quarters were supposed to be screened. The screening of the general convict quarters was incomplete and defective; that of the cottage occupied by the volunteers was carefully scrutinized and all defects repaired before beginning the study and kept so throughout.

Water Supply and Sewerage.—This was essentially the same for all sections of the population of the farm.

Disease Prevalence.—Pellagra is fairly prevalent throughout the county, but, so far as we could learn, no case of this disease had been observed on the farm.

External Communication.—Although an isolated community, the camp was in frequent communication with the outside world through visitors to the families of the officials and through visiting friends or relatives of the prisoners other than the volunteers. The needs of

the camp made it necessary also for officers or trusties to visit Jackson and other points beyond the farm. While no pellagrin is known to have visited the camp during the study, some of the free individuals or trusties may have come into direct contact with pellagra on the occasion of their visits beyond the farm. The volunteers, however, were segregated and under special guard, and no communication was permitted them with the outside except through one of us (G. A. W.) who resided at the camp throughout the study. While, therefore, some of the controls may have come into direct contact with pellagra, such contact was, we believe, absolutely excluded for the volunteers.

TABLE 1.—Approximate Composition of the Food Consumed by a Group of Convict Controls (Thirty-Four Men) During Week Ending July 26, 1915

Food	Quantity Consumed, Pounds	Protein, Pounds	Fat, Pounds	Carbohydrate, Pounds
Biscuit	197.62	17.19	5.14	109.28
Biscuit pudding	57.00	4.06	1.08	20.58
Flour cakes (fritters)	13.25	1.15	0.34	1.31
Corn bread	73.44	3.78	2.35	30.83
Grits	16.25	0.27	0.08	2.45
Rice	23.19	0.41	0.02	5.66
Butter	6.19	0.06	5.26	
Milk, skimmed	284.94	9.09	0.09	12.51
Eggs	2.37	0.31	0.22	
Brown gravy	8.19	0.11	0.08	0.09
Beef gravy	5.31	0.52	0.02	0.06
Beef hash	27.56	5.90	14.25	
Beef liver	1.75	0.26	0.08	0.03
Beef roast	13.12	2.02	3.75	
Salt pork	47.12	2.96	34.26	
Vegetable soup	50.62	1.47	0.10	0.25
Potatoes, Irish	127.12	3.17	0.13	26.57
Cabbage	15.00	0.15	0.05	0.84
Corn on cob	12.75	0.39	0.06	0.98
Cucumbers	6.52	0.07	0.01	0.17
Okra	22.12	0.15	0.24	0.71
Onions, raw	2.86	0.05	0.01	0.28
Peppers, sweet green	4.94	0.36	0.21	1.52
Tomatoes	17.62	0.21	0.07	0.69
Apple pie	17.50	0.54	1.72	7.49
Apples, baked	0.37	.....	.....	0.04
Apples, stewed	21.75	0.07	0.07	2.35
Sugar	34.75	.....	.....	34.75
Sirup, cane	48.75	0.23	.....	36.85
Total		57.47	70.13	296.79
Per man per day (gm.)		110	134	566

Hygiene.—The quarters of the convict controls were inadequately looked after and were for the most part dirty and vermin-infested. The practice of personal cleanliness was left to the individual, and, therefore, varied within wide limits. In contrast, the quarters of the volunteers were regularly and thoroughly cleaned and free of vermin.

Each volunteer was required to wash hands and face before each meal and to take a full bath at least three times a week.

Work.—The volunteers continued to do a share of the work of the farm. At first the hours of the volunteers were those of the other prisoners, but after beginning the experimental diet the hours were shortened, and when in the field they were allowed a rest period of ten minutes in every hour. The work of the convict controls is rated by us as requiring moderate to hard, that of the volunteers as requiring moderate to light muscular exertion.

Diet of Controls.—While it varied somewhat from week to week, the character of the diet of the convict controls during the second period of the study is fairly well illustrated in Table 1, for the week ended July 26, 1915. Weighings were made of the food consumed by a group of this class of controls during four sample periods of a week each. Chemical analyses were impracticable, and as in the case of some of the cooked dishes an estimate had to be made of the quantity in place of actual weighings of the individual ingredients; the composition shown in this table (computed by means of the Atwater and Bryant Tables [3]) is an approximation which, while probably fairly close, cannot be regarded as exact. Judged by the indications afforded by the four sample-week periods, summarized in Table 2, the diet of the controls, although tending to be rather high in fat, conformed fairly well to recognized standards. The potential energy varied between 3,500 and 4,000 calories. The intake of protein varied between approximately 90 and 118 gm., that of fat between 95 and 135 gm., and that of carbohydrate between 540 and 580 gm. Approximately, from 20 to 35 gm., or about 20 to 35 per cent. of the protein was from animal food.

TABLE 2.—Summary of Approximate Average Composition of the Food Consumed by Some of the Convict Controls Per Man Per Day During the Specified Sample Periods

Sample Period, Week Ended	Protein			Fat, Gm.	Carbohydrate, Gm.	Calories	Percentage of Total Calories Derived from Protein
	Total, Gm.	From Animal Food					
		Gm.	Percentage of Total				
June 6	88	29	33	97	568	3,500	10
June 29	97	25	26	117	520	3,695	11
July 26	110	22	20	134	500	4,020	11
Oct. 21	90	18	20	90	579	3,645	10

Experimental Diet.—The volunteers began the experimental diet with the midday meal of April 19, 1915, and continued it up to and including the midday meal of Oct. 31, 1915.

3. Bull. U. S. Department of Agriculture, No. 28.

The ingredients of the diet were white wheat flour, corn (maize) meal, hominy grits, cornstarch, white rice, granulated cane sugar, cane syrup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens and coffee. In the preparation of biscuits and cornbread "Royal" baking powder was used. Table salt and pepper were freely allowed for seasoning. Up to July 28, buttermilk was used in making the wheat biscuit, this being the same biscuit as that provided the controls. During the week ending June 27, 3 pounds of beefsteak were served at one of the meals, thus giving each man approximately 4 ounces of lean beef on this occasion. No fats other than those occurring naturally in the foods specified were used; the pork fat was extracted from salt pork by frying or boiling. The sirup was home-produced, from "ribbon" sugar cane raised on the farm.

All ingredients appeared to be of excellent quality and, with one or two exceptions, were part of the general camp supply. The principal exception was the maize meal. That of the camp was home-ground from corn raised on the farm and was unbolted. As it was desired to keep the antineuritic vitamin content of the diet low, and as it was believed that the milling might be a factor of importance in this and possibly other respects, we preferred to use a bolted meal, and accordingly provided the volunteers with such. Having in mind the great etiologic significance that had for so long attached to the quality of the maize, we provided the best quality of both meal and grits obtainable on the local market. In order that we might have a biologic check on the quality of these maize products, we arranged to secure our supply from part of that being used at one of the orphanages at which a study of the preventability of pellagra by diet was being made at the time and at which, it may be recalled, no pellagra occurred during 1915. For purposes of additional check, we arranged also that the controls should share with the volunteers the hominy grits thus provided.

The diet served was not absolutely uniform throughout the experimental period, as we felt it necessary by various devices to counteract, from time to time, the tendency of the volunteers to minimize the consumption of maize. There were also individual variations in the diet consumed resulting from individual variations in preference for different foods leading to a certain amount of trading of favorite dishes. Compared with the average diet we have in more recent studies [4] in cotton mill villages found associated with pellagra our experimental diet differed most notably from this in that it was very much more restricted, included no dried legumes, practically no animal

4. Goldberger, Wheeler and Sydenstricker: J. A. M. A. **71**:944 (Sept. 21) 1918; also, Public Health Rep. **35**:648 (March 19) 1920.

protein, and included relatively considerable quantities of green vegetables. So far as may be judged by such surface indications, our experimental diet was probably not altogether a typical or average one.

Weighings of food consumed were made for eight periods of one week each. Chemical analyses were impracticable so that the general composition of the diet was computed by means of the well-known Atwater and Bryant tables and the mineral constituents by means of the factors published by Sherman.[5] The results obtained for the week selected as fairly representative are shown in Table 3, and a summary for each of the weighing periods is shown in Tables 4 and 5. Reference to these shows a variation in energy intake of between about 2,500 and 3,500 calories, or a variation of between about 40 and 54 calories per kilo of the average weight of the volunteers. This it will be recognized compares favorably with the requirement by the organism of "35 calories per kilogram of body weight in the average man doing light work on a mixed diet."[6] About 6 per cent. of the calories were contributed by the protein.

TABLE 3.—Approximate Composition of the Food Consumed by the Volunteers During the Week Ending August 9, 1915. Average Per Man, Per Day

Article	Quantity, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Minerals (in Grams)*							
					Ca	Mg	K	Na	P	Cl⁻	S	Fe
Cornmeal	176.4	16.23	3.35	133.01	0.032	0.148	0.376	0.009	0.335	0.258	0.196	0.0016
Grits	35.1	2.80	0.25	27.59	0.004	0.020	0.061	0.007	0.051	0.016	0.048	0.0003
Wheat flour	166.9	18.02	1.84	124.84	0.032	0.080	0.192	0.100	0.154	0.124	0.295	0.0017
Rice	30.0	2.40	0.09	23.70	0.008	0.010	0.021	0.008	0.029	0.016	0.035	0.0003
Cane sirup	35.1	0.16	0.00	26.52	.....	.....	.....	.....	.....	.....	.....	.....
Cane sugar	72.5	0.00	0.00	72.50	.....	.....	.....	.....	.....	.....	.....	.....
Sweet potatoes	163.1	2.94	1.14	44.69	0.031	0.046	0.648	0.004	0.073	0.153	0.039	0.0008
Cabbage	15.8	0.25	0.05	0.87	0.007	0.002	0.039	0.004	0.005	0.004	0.010	0.0002
Collards	58.9	2.65	0.35	3.71	0.002	0.018	0.302	0.015	0.058	0.040	0.102	0.0011
Pork fat	105.9	0.10	105.65	0.00	.....	.....	.....	.....	.....	.....	.....	.....
**Total	859.0	46.00	113.00	457.00	0.170	0.270	1.640	0.270	0.710	0.610	0.730	0.0060

* Not including table salt or baking powder. **Total calories, 3,115.

The average intake of protein varied between approximately 41 and 54 gm., that of fat between 91 and 134 gm., and of carbohydrate between 387 and 513 gm. From 80 to 97 per cent. of the protein was from cereal sources; practically none was derived from animal food.

Comparison shows the experimental diet and the diet of the controls to be much alike with respect to intake of fat and carbohydrate, and when due allowance is made for the difference in the amount of work done by the contrasting groups, also with respect to energy.

5. Sherman, H. C.: Chemistry of Food and Nutrition, 1918, 2d Ed.
6. Lusk, Graham: The Elements of the Science of Nutrition, 1917, p. 345.

With respect to protein, however, there are some rather outstanding differences between the two. The intake of this nutrient by the convict controls was approximately twice that of the volunteers, and while from 20 to 35 per cent. of the protein in the diet of the former group was from animal sources almost none at all of that in the diet of the latter was derived from this class of foods.

TABLE 4.—SUMMARY OF AVERAGE COMPOSITION OF THE DIET OF THE VOLUNTEERS DURING SPECIFIED SAMPLE PERIODS (PER DAY)

Sample Period Week Ended	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Total Calories	Calories per Kg.	Percentage of Total Calories Derived from Protein
May 27	54	134	513	3,570	54	6
June 21	41	99	426	2,835	45	6
July 12	41	91	397	2,600	40	6
Aug. 9	46	113	457	3,115	49	6
Aug. 29	46	117	479	3,240	51	6
Sept. 13	47	119	481	3,295	52	6
Sept. 20	44	114	459	3,125	50	6
Oct. 6	44	106	479	3,120	51	6

TABLE 5.—SOURCES OF PROTEIN IN DIET OF THE VOLUNTEERS DURING SPECIFIED SAMPLE PERIODS (PER DAY)

Sample Period Week Ended	Total, Gm.	From Animal		From Cereal		From Other Foods	
		Gm.	Percentage of Total	Gm.	Percentage of Total	Gm.	Percentage of Total
May 27	54	1.5	3.0	44.0	81.0	8.0	16
June 21	41	1.4	3.4	33.0	80.5	6.6	16
July 12	41	0.9	2.0	37.0	90.0	3.0	8
Aug. 9	46	0.1	0.3	40.0	87.0	5.8	13
Aug. 29	46	0.1	0.3	42.5	92.0	3.4	8
Sept. 13	47	0.1	0.3	43.8	93.0	3.3	7
Sept. 20	44	0.1	0.3	40.5	92.0	3.0	7
Oct. 6	44	0.1	0.3	40.0	91.0	3.8	9

With respect to the mineral constituents and vitamins differences can be indicated in very general terms only. The inclusion of milk, butter, peas and beans in the diet of the controls and their complete absence (milk excluded after July 28) from the diet of the volunteers would suggest that the former had a more satisfactory mineral composition and was richer in both the fat soluble and the antineuritic vitamin.

RESULTS

Aside from a number of more or less ill-defined ailments and minor injuries, there were observed among our controls a number of rather sharp attacks of malaria, one of appendicitis with appendectomy, one of hemorrhoids with surgical operation, one of probable ureteral cal-

culus, and one of cerebral tumor, but in none was there any evidence justifying even a suspicion of pellagra. It was quite otherwise with the volunteers as may be seen from the following analysis of the manifestations observed among them. The detailed clinical record of each individual cannot, of course, be presented within the limits of the present paper, but will be found in our full report.

ANALYSIS OF SYMPTOMS

First Symptoms.—After instituting the test diet, no complaints to which we would attach any significance were recorded until May 2, when we have a complaint by "A. E. S." of weakness and dizziness. Six days later another of the volunteers, "A. W.," brother of the first, made his first complaint, that of epigastric pain. By June 20, all eleven men had begun to complain in one way or another. Eight of the eleven men made their first complaint between May 18 and June 20, that is, during the second month of the test diet. Of the symptoms first complained of, weakness, alone or accompanied by some other symptom or symptoms, was mentioned by five. Of the other six men, four mentioned abdominal discomfort or pain (epigastric or right iliac) and two mentioned headache (with nausea in one and "indigestion" in the other) as the first, or among the first, symptoms.

Weight.—All of the volunteers lost weight, the loss varying between 6 and 22.6 per cent. Comparison of the weight curves of the volunteers with those of a comparable group of controls discloses a very marked difference. The weights of all the volunteers show a general downward trend which is particularly marked during the last four weeks of the experiment. In the control group the weights tend to be stationary or a slight early downward trend is followed by an upward tendency; in none is there any significant loss during the last four weeks.

Weakness.—In all of the volunteers there developed clear indications of some diminution in strength and vigor. In some this loss was very conspicuous, being shown by an unsteady gait and, when standing, by a tendency to seek for the support of the back of a chair, a table, or a wall. Subjectively, all the men complained of a general weakness. In some there was the additional special complaint of weakness in the legs, and one complained of stiffness in the legs, of which, however, there was no evidence apparent to the observers. At the close of the experiment, all of the volunteers looked worn. In several the objective and subjective indications of weakness and exhaustion were very great, quite out of proportion to the actual loss in weight.

Headache.—Headache variously localized and of varying degree, both as to intensity and frequency, was complained of by seven of the volunteers.

Pain.—Painful sensations of one kind or another, other than headache, occurred in all eleven men. Pain in the small of the back and abdominal pain or discomfort were of about equal frequency, the former occurring in five and the latter in six of the men. Pain in the side was the next in order of frequency, being recorded in four of the volunteers. In three of these four subjects the pain was in the left side. In all four it was referred to the region of the costal border near the corresponding nipple, or mid-axillary, line.

Pain in the right iliac region [7] occurred in three cases, in the epigastric region (probably dyspeptic) in two, and in the hips in one case. Cramps in the legs and darting pains starting at the ankles and passing upward were complained of by one of the men.

Nervousness of varying degree was one of the most nearly constant of the manifestations recorded. It occurred in ten of the volunteers. *Vertigo* occurred in five cases. *Wakefulness* of varying degrees and for varying periods was complained of by five of the volunteers. In some of these, and at times in the others, it appeared to be brought about by some painful sensation (headache, etc.) in others, or at other times, there appeared to be no reason for it other than "nervousness" or restlessness.

Paresthesias.—Vague nervous manifestations that may be grouped as paresthesias were also noted. Burning in the "stomach" occurred in two cases, and burning in the feet and legs in one. A complaint of a feeling of heat was noted in one of the men. A sensation described as if an acorn had lodged in the chest was spoken of by one, and as if a "knot of something in the stomach" by another.

Mental Depression.—Apprehension and moroseness of a degree to be decidedly noticeable was recorded in one man.

The *knee jerk* became exaggerated in five of the eleven men. In one it appeared to be reduced and in five no change was recognized. Of the five that were exaggerated the change was noted October 17 in one, and October 24 in four; in all the change was first noted at or shortly after the close of the sixth month of the test diet.

Digestive Tract.—Reddening of the tongue at tips and margins was noticed in five of the men. In two of these there was also some reddening of the mouth. In all instances the reddening of the tongue was slight to quite moderate in degree. Burning of the mouth was reported

7. This pain is very suggestive of appendicitis and we have some reason to believe has occasionally led to operation. The surgeon will do well to keep in mind that pain in the right iliac region may be associated with pellagra.

by one of the men, and in another there was noted a slight increase in the salivary flow. Although complaints of diminished appetite were made at one time or another by nearly all of the volunteers and was fairly marked in at least three of the men, they all, nevertheless, ate fairly well.

Dyspeptic symptoms, including gaseous or acid eructations, were noted in at least five of the men. Vomiting occurred in four and nausea without vomiting was noted in two of the subjects. Gastric analyses were not practicable.

A mild diarrhea, up to three or four watery evacuations a day, occurred in three and a tendency to constipation was noted in one of the men. In seven no change from the normal was noted.

Skin.—A reddening of the oral commissures with tendency to fissuring was noted in one, and in a second, besides the reddening, there was noted an actual fissuring with a somewhat linear erosion extending for about one centimeter downward and backward on the cutaneous surface.

A well marked dermatitis varying somewhat in extent but bilaterally symmetrical, sharply marginated and more or less scaly developed on the ventral or ventrocaudal surface of the scrotum of each of six of the volunteers. The skin of the median raphé retained a normal appearance in all instances. A fairly definite bilateral erythema affecting the scrotum was noted in a seventh and a doubtful erythema on the scrotum of an eighth man. The earliest date of the beginning of this eruption was September 12, or at about the end of the fifth month of the diet. The evolution of these lesions (scrotal) was at first rather slow, so that it was not until very near to the end of the experimental period that they became sufficiently well-defined to permit of more than a suspicion of their significance. In some of the cases this dermatitis was accompanied by slight itching and burning. In one man there were no subjective local sensations, and the lesion on the scrotum might have escaped observation had we not made our examinations after completely stripping each man.

In three of the cases with lesions on the scrotum the erythema or dermatitis extended in some degree to the under surface of the penis, and in two of these there was also some involvement of the prepuce.

In addition to the lesions on the genitalia, three of the men presented lesions on other parts. One presented a slight erythema over the knuckles of the middle and ring fingers of both hands, to which our attention was first called by Professor Haase, one of our dermatologic consultants, one presented a very well marked, indeed, a classical, pigmented, keratosed, bilaterally symmetrical dermatitis of the backs of the hands, and the third a well marked erythema of the dorso-

lateral areas of the deeply tanned skin of the neck.[8] The volunteer presenting the lesions at the oral commissures presented no other cutaneous lesions. The classically marked dermatitis on the back of the hand, though later in appearing, was of much more rapid evolution than that on the scrotum. This and the case with the erythema on the sides of the neck confirmed our interpretation of the nature of the genital (scrotal) lesion in these and the other cases.

With respect to *temperature* and *pulse* our data are in such form as to permit only of the general statement that these showed no notable deviation from the normal.

Palpitation was complained of by two of the men; this should probably be considered a manifestation of indigestion.

Urine.—The conditions under which we worked made it impracticable to regularly secure twenty-four-hour specimens, so that with but few exceptions the urine sample represented that first passed in the morning. The results of the examinations of these specimens can, therefore, be interpreted only in a very general way. In all instances there was a more or less marked trend to a reduced acidity. A tendency to reduced specific gravity was also suggested, but this was not clear. We found indican in the urine of at least seven of the volunteers during the period of the test diet. In six of these it had also been present before that period; whether this was also the case in the seventh we cannot say, as no examination was made in this instance prior to the beginning of the experimental diet. In four of the volunteers indican was detected in the urine before beginning the diet, but none during the course of the experimental period; in two of these indican reappeared in the specimen passed about eighteen hours after return to a high animal protein diet. In one albumen present during the preliminary period disappeared after about two months of the test diet.

Diagnosis.—The volunteers were seen with us on three occasions and a diagnosis of pellagra concurred in, in six of the men, by Dr. E. H. Galloway, then secretary of the Mississippi State Board of Health, and by Dr. Nolan Stewart, one time superintendent of the Mississippi Asylum for the Insane at Jackson, and among the first to recognize pellagra in Mississippi.

8. In this connection the following from a letter from Professor Haase, referring to one of the volunteers seen by him in Memphis shortly after the latter's release, is of interest: "He had not only a sharply marginated pigmented lesion on the left side of neck, but two pigmented lesions on right hand over the articulations." Unfortunately, Professor Haase was unable to furnish the name of this man so that he cannot be identified definitely. We think it probable, however, that this refers to volunteer "E. W. H.," in which event the lesion on the right hand had escaped our observation or had developed after his release.

In excluding the known dermatoses other than pellagra, the special knowledge of Dr. Marcus Haase, professor of dermatology in the Medical College of the University of Tennessee, Memphis, Tenn., and that of Dr. Martin Engman, professor of dermatology in the Washington University Medical School, St. Louis, Mo., were utilized in consultation. In addition to the foregoing, who were formally called into consultation, the subjects were also seen by Drs. C. R. Stingily and F. L. Watkins of the State Board of Health, and by Dr. C. H. Waring of the U. S. Public Health Service, all of whom concurred in the diagnosis. In this connection it may be stated that in response to an inquiry (August, 1918) addressed to our dermatologic consultants as to whether they were still of the opinion that the known dermatoses other than pellagra could be excluded in our experimental cases, Professor Engman writes (Sept. 4, 1918): "Will say that I am at present even more confirmed in the opinion I gave you three years ago, as to the nature of the eruption on the convicts in the experimental squad, than I was at that time," and Professor Haase, under date of Aug. 20, 1918, writes: "I have not changed my opinion in regard to cases seen with you and Wheeler at the prison farm near Jackson, Miss. As stated to you then, I knew of no dermatologic condition, except pellagra, that would produce lesions seen, and on my return home looked for early lesions occurring on scrotum and observed two such cases." We may add that in the four years since the close of the experiment we have seen many hundreds of cases of pellagra (over a thousand cases were seen by us in a cotton mill village study in South Carolina in 1917 alone) and this exceptionally large experience with all types of cases has afforded ample additional confirmation of the soundness of our diagnosis in our experimental cases.

It is a not infrequent observation that in a family of several members, although only one may show the distinctive cutaneous lesions, some, if not all, of the others may present subjective and other manifestations which leave little room for doubt that they also are suffering from the same disease. Now, it seems to us, that our squad of volunteers is strictly comparable to a family group, so that it would appear to follow that, having recognized the six cases presenting the skin lesions as pellagra, this diagnosis may properly be extended to apply to the five without the distinctive cutaneous lesions, but presenting the other manifestations. In other words, we are of the opinion that every one of the volunteers developed pellagra, at least six with skin lesions and four or five without ("pellagra sin pellagra").

Discussion.—The fact of the first appearance of the skin lesion on the scrotum in all our cases with definite eruption, suggested to us that the scrotal lesion might be a much more common early skin manifesta-

tion than had theretofore been believed. The literature on this point, at the time of the publication of our preliminary note was, and still is, extremely meager. There existed, so far as we are aware, only two first hand reports of this lesion, a paper by Deiaco [9] and a report by Stannus.[10] In the one case reported by Deiaco the scrotal eruption was not the initial one, but was preceded by lesions in other locations. Although Merk, by implication, clearly suggests [11] that the scrotal lesion may be the first to appear, Stannus seems to have been the first to actually record such cases. In his report of pellagra in Nyasaland, Stannus records nineteen cases (out of 100 with eruption) that presented the scrotal lesion, and of these nineteen, four presented the scrotal lesion alone; whether the scrotal lesion was the first to appear in any other of his cases is not clear from his report. Since the publication of our note a case of pellagra with the initial lesion on the scrotum has been reported by Crosby [12] from South Carolina, and by Wood [13] from North Carolina.

In the course of our study of pellagra in cotton mill villages in South Carolina in 1916, notes were made (by G. A. W.) of twenty-three male cases examined for lesions on the genitals and of finding four with lesions on these parts as the initial site. Of these four cases, one was a first and three were recurrent attacks. Of the twenty-three cases examined, eight were claimed to be first and fifteen recurrent attacks, so that we had one of eight first attack cases with the initial site of the dermatitis on the genitals and three of fifteen recurrent attack cases with this lesion.

This experience would seem to bear out our suggestion that the pellagrous eruption occurs on the male genitalia as an initial lesion much more commonly than the literature might lead one to judge. It remains a fact, however, that the genital lesion, whether early or late, is a somewhat unusual one. Its appearance in all our cases with eruption as the initial lesion is therefore of exceptional interest. It is extremely difficult if not impossible to interpret this as merely a chance phenomenon or as an individual peculiarity. We are inclined to interpret it as a specific reaction, direct or indirect, to some special factor or combination of factors in the diet, and it suggests to us further

9. Deiaco, Pius: Ueber lokalisation und natur der pellagrösen hautsymptome, Wien. klin. Wchnschr. **20**:967, 1907.

10. Stannus, Hugh S.: Pellagra in Nyasaland, Tr. Soc. Trop. Med. and Hyg. **7**:32, 1913.

11. Merk, Ludwig: Die Hauterscheinungen der Pellagra, Innsbruck, 1909, p. 20.

12. Crosby, C. E.: Pellagra with Erythema of Scrotum as Initial Skin Manifestation, J. A. M. A. **68**:1403 (May 12) 1917.

13. Wood, E. J.: The Diagnosis of Pellagra, Arch. Diagnosis, **10**:139 (April) 1917.

that the site of at least the initial lesion in pellagra is bound up with a specific quality of the diet. Thus, we are inclined to believe that the dietary fault related to a case of pellagra with the initial lesion on the backs of the hands differs in some essential detail from that associated with a case in which the initial lesion appears on the backs of the feet, etc. It seems to us that we have here, at least, one element in the explanation of some of the reported differences in the manifestations of pellagra in different localities and in the same locality in different years.

CONCLUSIONS

Having due regard for the controlled conditions of the experiment, the conclusion would seem to us to be warranted that pellagra developed in at least six of our eleven volunteers as the result of the restricted diet on which they subsisted.

In considering its significance in relation to the etiology of the disease this experiment should be regarded as evidence not apart from but in conjunction with other evidence bearing on this problem. When so considered it is our judgment that this evidence clearly and consistently points to diet as the controlling factor in the causation as well as in the prevention of the disease. We have elsewhere considered at some length the more important evidence in favor of an essential infective etiological factor in this disease.[14] We shall, therefore, confine ourselves here to a consideration of only one of the arguments frequently advanced in its favor. This most commonly takes the following form:

"Inasmuch as bread lines and poor nutrition are of common occurrence in such large cities as New York, Chicago, etc., and as pellagra is of rare occurrence in these places, diet and poor nutrition can have nothing to do with pellagra." More recently this argument has at times been stated as follows: "Inasmuch as the people of Europe, particularly of the Central Powers, have been on starvation diets and necessarily badly nourished, and we hear of no pellagra among them, diet and poor nutrition can have nothing to do with pellagra." Assuming the facts to be as stated, the fallacy in the argument at once becomes apparent when it is pointed out that beriberi, a disease well known to be dependent on a faulty diet, seems to be or to have been no more prevalent than pellagra under the circumstances mentioned. Evidently, then, it does not necessarily follow that, because a disease is the result of a faulty diet, any faulty diet will bring it about. What this argument does suggest, and strongly, is that if poor nutrition favors infec-

14. Goldberger and Wheeler: Bull. Hygienic Laboratory, No. 121; also, Goldberger, Wheeler and Sydenstricker: Public Health Rep. **35**:648 (March 19) 1920.

tion, as is so commonly suggested, then either (1) "poor nutrition" does not predispose to invasion with the hypothetical "infection" of pellagra, or (2) no such "infection" exists, or finally (3) that a specific kind of poor nutrition is necessary to permit the pellagrous "infection" to establish itself.

In considering these possibilities, it may be argued that "poor nutrition" does favor invasion with the hypothetical pellagrous "infection" in localities where this "infection" is present in the environment. This would imply that in New York and Chicago, and, incidentally, in our North, as a whole, the pellagrous infection is absent or held in restraint by some unknown factor. As a matter of fact, cases of pellagra, though relatively rare, are by no means of infrequent occurrence in our Northern states and in such cities as New York, Chicago, etc. The hypothetical infection of pellagra is present, therefore, and, it may be added, has been present in this environment at least since the notable epidemic of 1909 at the Peoria (Ill.) State Asylum. Consequently, the important question presents itself: Why is the disease no more prevalent in these cities and in the North generally if poor nutrition favors its invasion? The restraint imposed by the cooler northern climate, the only explanation which suggests itself and one frequently advanced in favor of the relative rarity of the disease in the North, fails as the explanation when it is recalled that in Italy pellagra has for generations been chiefly, if not entirely, prevalent in the cooler northern mountainous section, and that the disease has long been highly endemic in such relatively rigorous climates as those of Bukowina, Transylvania, Roumania and Bessarabia.

In view of these facts, it seems to us that the assumption that "poor nutrition" of a general character favors invasion with the hypothetical "infection" of pellagra, and that this is the explanation of the rôle of diet in pellagra, is untenable. This does not, however, in strict logic exclude the third of the above stated possibilities, namely, that a poor nutrition of a specific kind is essential to enable this "infection" to establish itself. It will at once be recognized that this is identical with the view still held by some with reference to the etiology of such diseases as beriberi and scurvy, namely, that each is due to a specific infection which can arise only in one subsisting on a deficient diet of a specific character.

As in beriberi and scurvy, however, no unequivocal evidence in support of the existence of an essential infective factor in pellagra has yet been adduced. Nevertheless, if in spite of this fact and in spite of the evidence demonstrating the vital rôle of diet in these diseases, one still considers it logical to hold that there is also a second essential extrinsic factor, an infection, in beriberi and likewise one in scurvy, we recognize that it is equally logical to hold a similar view with respect

to pellagra. Clearly, however, even in such event diet is necessarily recognized as the primary controlling element.

DIETARY FACTORS

Having evaluated the controlling etiologic influence of diet, we may next seek to determine the factor or factors in the diet which are to be charged with bringing about the pellagra syndrome or syndromes. We have already seen that as relates to quantitative intake of energy, fat, carbohydrate and protein, the experimental diet differed from the diet of the controls significantly only in that the intake of protein was low, though within the limits of recognized standards. These characters of the diet would seem therefore not to be of primary importance, an interpretation which is supported by the results of our studies of the food supply of pellagrous households in cotton mill villages.[15] With respect to the more intimate make-up of the diet, it has previously been noted that the protein was almost exclusively from products of highly milled cereals (wheat, maize, rice). In the light of recent studies, notably those of Osborne and Mendel and of McCollum and associates, this would suggest the probability of a deficiency in intake of some one or more of the amino acids, a probability that would be much increased by the low plane of protein intake. This interpretation is strengthened by the indications afforded by the results of some feeding experiments in rats carried out by Sullivan (Hygienic Laboratory Bulletin No. 121) at the U. S. Pellagra Hospital at Spartanburg, S. C., pointing to the protein as one of the limiting factors of the diet for this species.

The antineuritic vitamin content of the diet was planned to be low and feeding experiments by Sullivan show that the diet was actually deficient in this factor for the common fowl and the pigeon. It is of great interest to note, however, that none of the subjects developed any distinctive clinical manifestations of beriberi; whether they would have done so eventually had they continued on the diet is an interesting speculation.

Judging by the fact that none of the men showed the slightest recognizable indications of scurvy the content of the diet in the antiscorbutic factor would seem to have been adequate for the period of the experiment at least.

With regard to the adequacy of supply of the fat soluble vitamin, it is difficult to judge by reason of the meagerness of the available fundamental data; none of the men developed any eye symptoms currently considered suggestive of a deficiency in this food essential.

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15. Goldberger, Wheeler and Sydenstricker: J. A. M. A. **71**:944 (Sept. 21) 1918; also, Public Health Rep. **35**:648 (March 19) 1920.

Compared to the average intake afforded by various American dietaries as compiled by Sherman,[16] the intake of some, at least, of the mineral ingredients in the diet of our volunteers was decidedly low But whether the mineral intake as a whole or in any of its constituents was actually inadequate or improperly balanced for normal nutrition, it is perhaps impossible to state at the present time; that such may have been the case is rather strongly suggested, however.

It would seem from the foregoing considerations that our test diet was probably faulty in some degree with respect to the protein (amino acid or acids) antineuritic vitamin and mineral constituents. McCollum,[17] as a result of his extensive studies in rats, believes that our diet was also deficient in the fat soluble vitamin. Judging by the results of our field and other observations with reference particularly to the inclusion of dried legumes in the diet of pellagrous households and of individuals, we are satisfied that a deficiency in the antineuritic vitamin is not an essential element in the pellagra producing dietary fault. Similarly the recent observation of the failure to prevent the disease in two individuals who for periods of four to five months before developing the eruption daily consumed the fat soluble vitamin contained in three ounces of creamery butter [18] would seem to indicate that a deficiency in "fat soluble A" is not essential to the production of pellagra. The evidence that we have elsewhere adduced [15] of the preventive value of a meat supplement, coupled with the seemingly small importance that attaches to this food as a source of minerals, would tend to indicate that the mineral factor is of no essential etiological importance. On the other hand, it may be pointed out that the sharp decline in seasonal incidence of the disease, in cotton mill villages of South Carolina, at least, is associated with a great increase in the food supply of green vegetables, a class of foods recognized as important sources of ash constituents in the diet. The facts at hand, therefore, do not warrant a definite judgment on this point. So that of the now generally recognized essential dietary factors, there remain for consideration as possibly essential in relation to the etiology of pellegra, the protein (amino-acids) and the inorganic factor. The determination of which or what combination (or combinations) of these, if any, or whether some deficiency in an as yet unknown dietary factor (vitamin?) alone or in some combination or combinations with one or both of these known factors constitutes the specific pellagra producing dietary defect or defects must await further study.

16. Op. cit., p. 271.

17. McCollum and Simmonds: J. Biol. Chem. **32**:29, 1917.

18. Goldberger and Tanner, unpublished data. The amount of fat soluble vitamin derived from other sources during this period is believed to have been negligible.

SUMMARY

1. An experiment was carried out at the Rankin farm of the Mississippi penitentiary to test the possibility of producing pellagra in previously healthy men by feeding a monotonous, principally cereal, diet.

2. The subjects of the experiment were eleven white adult male convicts who volunteered for the purpose. They were segregated and kept under special guard. None gave a history of having had pellagra or of the occurrence of this disease in any member of the family or a near relative.

3. All persons other than the volunteers resident on the farm were under observation as controls. This included 108 convicts, of whom thirty-five were under observation for a period comparable to the period of observation of the subjects of the experiment. In addition there were twelve free persons who were present throughout the study; included in these were four adult females and two children.

4. The general sanitary environment was the same for subjects and controls. With respect to personal cleanliness, cleanliness of quarters, and freedom from insects and vermin, the volunteers were decidedly better off than the convict controls.

5. No direct communication with the outside was permitted the volunteers. There was no special restriction imposed on the controls, convicts or free. Direct exposure of some of the controls to a hypothetical infection was possible and may have occurred when beyond the limits of the farm; this possibility is believed to have been excluded in the case of the subjects of the experiment.

6. The volunteers continued to do a share of the work of the farm, but, when compared with the convict controls, they had shorter hours of work and had regular rest periods when in the field. The work of the convict controls is rated as requiring moderate to hard, that of the volunteers as moderate to light muscular exertion.

7. The study falls into two periods, one extended from February 4 to April 19, during which the volunteers were kept under observation without any change in the regular prison fare; the second period extended from April 19 to and including October 31, during which the volunteers subsisted on the experimental diet.

8. The average intake by the convict controls, as shown by four periods of a week, each varied between approximately from 3,500 and 4,500 calories, between 90 and 110 gm. of protein, 95 and 135 gm. of fat, and between approximately 540 and 580 gm. of carbohydrate. Approximately from 20 to 35 per cent. of the protein was from animal food.

9. The ingredients of the experimental diet were highly milled wheat flour, maize meal and grits, cornstarch, white rice, cane sugar, cane sirup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens, coffee, "Royal" baking powder, salt and pepper. During the first three months some buttermilk was used in making wheat biscuits. All ingredients were believed to be of excellent quality and, with one or two exceptions, were part of the general camp supply. In its essential make-up the experimental diet was probably not entirely typical of the average pellagra producing diet.

10. The average intake by the volunteers, as shown by eight periods of a week each during the experimental period, varied between 2,500 and 3,500 calories, between 41 and 54 gm. of protein, between 91 and 134 gm. of fat, and between 387 and 513 gm. of carbohydrate.

11. Although both classes of controls (convict and free) were exposed to the chance of direct contact with pellagra and although, as compared with the volunteers, the convict controls were at a disadvantage hygienically, and were required to work harder and furthermore, although various minor ailments and a number of rather sharp attacks of malaria were observed among them, none of the convict (or other) controls developed any evidence of pellagra. On the other hand, although segregated and under special guard and the possibility of direct contact with pellagra excluded, and although under much more favorable hygienic conditions, not less than six of the eleven volunteers who remained in the test to the end developed evidence which experienced observers joined with us in recognizing as those of pellagra.

12. Significant subjective symptoms made their first appearance among the volunteers during the second month after beginning the test diet. These included weakness, abdominal discomfort or pain and headache. All subjects lost weight, the loss becoming particularly marked during the last four weeks of the experiment. At least six of the eleven men developed a well-marked eruption. The earliest date of the beginning of this was September 12, or at about the end of the fifth month of the diet. The initial site in all of the cases was the scrotum; later classical lesions also developed in one on the hands and in another on the neck. The knee jerk became exaggerated in five of the men, the earliest date being October 17, at the close of the sixth month of the experiment.

13. Having due regard for the controlled conditions of the experiment, the conclusion seems warranted that pellagra developed in at least six of our eleven volunteers as the result of the diet on which they subsisted.

14. The scrotal lesion is a much more common early skin manifestation of pellagra than has heretofore been realized, but is nevertheless a somewhat unusual one.

15. It is suggested that the site of at least the initial dermatitis accompanying an attack is bound up with a specific quality of the diet. The view is advanced that there exist essential differences in the intimate make-up of the diet corresponding to observed differences in some, at least, of the clinical types of the disease.

16. In relation to the production of pellagra, the dietary factors to be considered as possibly essential are (1) an amino-acid deficiency, (2) faulty mineral supply or constitution and perhaps (3) an as yet unknown (vitamin?) factor. As to which or what combination, or combinations, of these constitutes the specific pellagra-producing dietary defect or defects remains to be determined.

The experiment herein described was made possible by the hearty cooperation of Governor Earl Brewer and Dr. E. H. Galloway, of the State Board of Health of Mississippi, to both of whom our grateful acknowledgments are due. We are indebted to Dr. Galloway also for his interest and aid as one of our consultants. Our thanks are due also to Dr. Nolan Stewart and Professors Haase and Engman for their valuable assistance as consultants. To Dr. A. G. McLaurin of Brandon, Miss., prison physician since 1909, we are indebted for information relative to disease prevalence at the prison farm and to Drs. Stingily, Watkins and Waring we are indebted for their interest and for many helpful courtesies.

EXPERIMENTAL PULMONARY EDEMA*

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The following summary of the literature on pulmonary edema is to serve as a background for the present great interest in pulmonary edema stimulated by the work done on gas poisoning in the battle areas and in the laboratories. It was decided that the purpose of our work could be best fulfilled if an accurate recital of the experiments and data on experimental lung edema were chronologically arranged. The interjection of personal opinion and interpretation, therefore, is reserved until after the recital of the data.

In a study of the papers which might give information concerning the cause of pulmonary edema, it was found that the results could be grouped in the following order: (1) Lung edema occurring as an incident in an experiment; (2) lung edema produced for study; (3) lung edema recognized as a feature in an experiment, but its immediate cause overlooked or neglected. For this review, the second group is, of course, the most instructive and most deserving of attention, while the other two groups are suggestive.

HISTORICAL REVIEW

Virchow,[1] in 1853, produced pulmonary edema by injecting fat into a jugular vein. The mechanism was not investigated.

Pokrowsky,[2] while studying carbon monoxid poisoning in cats, dogs, rabbits and frogs, occasionally obtained lung edema. He was confirmed by Friedländer and Herter.[3]

Falk[4] studied the effect of gases and poisons on the glottis primarily. He was interested in the occurrence of spasm, and observed lung edema in mammals during chlorin gas poisoning.

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*The data in this paper were prepared originally for the Chemical Warfare Service as confidential matter in furthering the study of toxic war gases. Permission to publish has been granted.

1. Virchow: Virchows Arch. **5**:308, 1853.
2. Pokrowsky: Carbon Monoxid Poisoning, Virchows Arch. **30**:525, 1864.
3. Pokrowsky, Friedländer and Herter: Carbon Dioxid Rich Atmosphere to Rabbits Get Various Grades of Pulmonary Edema, Cohnheim's Allg. Path., Ed. 2, **1**:502; **2**:273, 1882.
4. Falk: Spasmus glottidis bei gewaltsamen Todesarten, Viertelj. gericht. med. **16**:6, 1872.

Friedländer[5] ligated the ascending aorta proximal to the innominate artery in the rabbit. The animal died in a short time and postmortem examination showed lung edema.

Longet[6] (from Chemery) noted the occurrence of lung edema after vagal section. (See also von Frey.[7])

Schweninger[8] noted that fat emboli led to acute lung edema. This was confirmatory of Virchow's work.

Lassar[9] studied the effects of acid vapors, nitric, sulphuric and hydrochloric, and of iodin on dogs and rabbits. The vapors rarely induced a bronchitis or a bronchopneumonia when sufficient air was mixed with them. In a few instances, lung edema occurred after asphyxia. He noted the nonappearance of acids in the urine, and stated that either the acids do not diffuse through the alveolar walls, or they are precipitated higher up in the respiratory passages, in which case they may unite with the lung epithelium before they can get through. Their danger lies in the fact that they lower the oxygen percentage of the inspired air, producing asphyxial symptoms.

Cohnheim and Lichtheim,[10] morphinized or curarized dogs and rabbits, and then injected enormous quantities (from 64 to 92 per cent. of the body weight) of a 0.6 per cent. solution of sodium chlorid at body temperature intravenously. In several cases, exitus occurred in a few hours with symptoms of acute pulmonary edema. The dogs had a decreased dry weight of the blood. Arterial pressure was increased temporarily or not at all, while the venous pressure rose slightly or not at all, but never came back to zero if it did rise. The pulse frequency was not increased. There was an increased velocity in the blood stream, and an increased lymphatic flow. There was a marked outpouring of fluid in the glandular organs, although none in the skin, central nervous system, or thoracic cavity. The blood count was uniform in the portal, jugular and femoral vessels. They say that venous stasis is not responsible for the edema. They also injected distilled water, a 3 per cent. glucose solution, various salt solutions and diluted blood serum, and obtained similar results. Merely replacing the blood was negative. Their view is that the capillaries vary in permeability, and they felt that this was proven by obtaining skin edema in these animals after wounding the skin, or painting it with iodin, or exposing the shaved abdomen to the sun's rays.

5. Friedländer: Untersuchungen über die Lungenentzuendung, Berlin, 1873.
6. Longet: Physiologie, Ed. 3, **2**:507, 1873 (see Chemery).
7. Von Frey: Die Pathologischen Lungen-Veränderungen nach Lähmung der nervi vagi, Leipzig, 1877.
8. Schweninger: Aertzliches Intellig. Blatt, 1876.
9. Lassar, O.: Ueber irrespirable Gase, Ztschr. f. Physik. Chem. **1**:165, 1877.
10. Cohnheim and Lichtheim: Ueber Hydrämie, Virchows Arch. **69**:106, 1877.

Welch,[11] in the *first extensive research on pulmonary edema* per se, raised issues which challenged the attention of many workers. He reviews the causes of pulmonary edema postulated by others, such as increased heart activity, direct irritants, collateral hyperemia, thinning of the alveolar air, effect of cold drinks, inflammatory conditions, stasis—pulmonary vein obstruction or weakened heart action with both chambers equally weak. He says that the mechanical factors have not been exhausted, and that a stasis edema is possible by the production of obstructions in the lung veins, left auricle, left ventricle and aorta. He produced lung edema in dogs and rabbits, more easily in the latter. Tying the aortic arch between the innominate and left subclavian arteries produced lung edema in only one rabbit, while tying two additional branches of the innominate artery resulted every time in lung edema accompanied by asphyxial phenomena. It requires almost complete occlusion of the aorta between the heart and the innominate artery to get an edema. Lung edema occurred when the pulmonary artery pressure rose. The carotid pressure usually rose. The stasis occurs because more blood goes to the heart than comes away, and the stasis is not due to weakness of the right ventricle. These methods, however, he says, are not applicable to human cases, nor are they comparable to what occurs in the human being. Ligation of pulmonary veins must be extensive before edema occurs, while pulmonary artery pressure rises slightly until the onset. Welch emphasized the fact that marked pressure on the left auricle and left ventricle produced lung edema in the rabbit. The microscopic picture resembles that found in man. Welch postulated a disproportion between the working power of the ventricles with the left less efficient than the right. He attempted to produce a onesided cardiac paralysis by the use of potassium, iodin, salts, carbon monoxid and strychnin internally, while potassium salts, chloroform, ice and heat were applied externally. At last, he succeeded in producing such a paralysis by squeezing the left ventricle of rabbits with his fingers. He never obtained edema by pressure on the right ventricle alone, or by pressure on the right and left ventricles. He believes that the increased capillary pressure in the lung vessels is added on to the greater permeability of the lung capillaries. Too much emphasis should not be laid on the fact that the pulse is weak in some human cases. Microscopic section showed distended capillaries filled with red blood corpuscles. Red blood cells were also found in the interstitial tissue.

Rosenbach,[12] while studying artificially produced valvular insufficiency, obtained pulmonary edema in two cases. His postmortem

11. Welch: Zur Pathologie des Lungenödems, Virchows Arch. **72**:375, 1878.
12. Rosenbach, O.: Ueber Artifizielle Herzklappenfehler, Arch. f. Exp. Path. u. Pharm. **9**:1, 1878.

examination findings inclined him to accept Welch's view of unequal activity of the ventricles.

Lichtheim[13] produced pulmonary edema in rabbits by ligation of the artery and veins at the hilus. This occurred when the ligation was done unequally, by which he meant that the inflow had not ceased while the venous outflow had. These lungs had the same appearance as in those experiments in which only the pulmonary veins were tied.

Mayer[14] confirmed Welch's findings. Ligation of the innominate and left subclavian arteries in noncurarized animals leads in most cases to marked edema with strong convulsions. In curarized animals no such results follow. He quotes Kussmaul and Teuner who produced pulmonary edema by ligating the arteries going to the head as indicating the importance of asphyxia as a cause of edema. Mayer obtained some results by ligating four main aortic branches. He believes that the variation in intensity of edema is due to (1) increased vascular tension, (2) vessel tonus, and (3) the milking effect of the right ventricle; and that these factors are especially present when asphyxial convulsions occur. Opening the abdomen and combining vessel ligation with the production of a double pneumothorax, so as to eliminate the mechanical effects of convulsions, prevented the occurrence of edema.

Sahli[15] endeavored to repeat Welch's results, but failed in most cases. In some cases, ligation of the aorta and pressure on the left auricle produced a rise in pulmonary artery pressure, followed by a lung edema in dogs and rabbits. He says, however, that such methods are crude and not applicable to human conditions. He minimizes convulsive factors on the basis of strychnin experiments in which he got high lung artery pressures. Even when the pulmonary artery pressure is high and the carotid pressure is low, no edema need result. Cohnheim, in 1876, showed that marked changes in the systemic circulation have little effect on the pulmonary circulation. A paralysis of the left ventricle need not produce lung edema in dogs. Pressure, clamping, isolated faradization, narrowing of coronary vessels and injection of cardiac poisons were all negative. In man, he reiterates, lung edema is possible where *both* ventricles are *weak*, as in a case of combined aortic and mitral insufficiency. Then, again, a majority of the lung edemas in man are of inflammatory origin in the lung itself. His experiments with hydrocyanic acid were negative.

13. Lichtheim: Versuche über Lungenatelektäse, Arch. f. Exp. Path. u. Pharm. **10**:71, 1879.

14. Mayer, Sigmund: Experimentale Pathologie des Lungenödems, Sitz. Berichte d. k. Akad. d. Wissensch. Wien. **77**: Part 3.

15. Sahli: Zur Pathologie und Therapie des Lungenödems, Arch. f. Exp. Path. u. Pharm. **19**:433, 1885.

Martin,[16] perfusing the mammalian heart with defibrinated blood, notes the frequent, unfortunate interruption of the experiments by the onset of lung edema. He was primarily interested in the activity of the heart itself.

Tigerstedt and Santesson[17] filled freshly removed frog's lungs with 0.6 per cent. sodium chlorid solution and found that they withstood a pressure of 14 mm. Hg for several hours, whereas, if the lungs were injured by heat, or by pouring into them distilled water or frog's bile, filtration is obtained at once.

Lehmann[18] obtained lung edema by exposing cats, rabbits and guinea-pigs to hydrochloric acid and ammonia vapors. He includes a microscopic description of the lungs. Lehmann probably deserves credit for his prophetic insistence that poisonous (irrespirable) gases deserve and require intensive experimental study with the development of proper technic. He quotes and criticizes Eulenberg,[19] Lewin[20] and Hirt.[21] The work of Hirt is discredited by him, even though Hirt was widely quoted as an authority at the time. Eulenberg studied a number of irritating gases somewhat superficially, he says, and without proper attention to oxygen supply and carbon dioxid removal. Lewin is at fault because he uses Hirt's data. Lehmann experimented with a gas mask in a gas-filled room. His experimental method provided oxygen supply and carbon dioxid removal by means of a modified Pettenkofer-Voit respiration chamber. It may here be stated, that many of his reports on gas effects state the mere fact that a lung edema occurred, but there is little attempt to study the sequence of symptoms, their interrelation, significance and cause singly.

Pettenkofer[22] reported the studies on irrespirable gases of his pupils (Gruber, Ogata, Lehmann, Nakahama and Mori) to the Munich Academy of Scientists. He emphasized Lehmann's results on guinea-pigs, cats, rabbits and man. Lung edema appeared with toxic doses of hydrochloric acid, ammonia, chlorin, bromin, hydrogen sulphid, carbon disulphid and anilin. Nitrobenzol was negative. The toxicity of all

16. Martin: A New Method of Studying the Mammalian Heart, Studies from Biological Laboratory, Johns Hopkins University **2**:118, 1882.

17. Tigerstedt and Santesson: Bignang. till. K. Svensk. Vet. Akad. **11**: No. 2, 1886.

18. Lehmann, K. B.: Experimentelle Studien über den Einfluss technisch und hygienisch wichtiger Gase und Dämpfe auf den Organismus (Ammoniak und Salzsäuregas), Arch. f. Hygiene **5**:1, 1886.

19. Eulenberg: Die Lehre von den Schaedlichen und giftigen Gasen, Braunschweiz, 1865; Gewerbe Hygiene, Berlin, 1876. See Reference 18.

20. Lewin: Lehrbuch der Toxicologie. See Reference 18.

21. Hirt: Die Gasinhalations Krankheiten, Breslau, 1873. See Reference 18.

22. Pettenkofer: Ueber Gesundheitschädlichkeit mehrerer hygienisch u. technisch wichtiger Gase und Dämpfe, Sitz. berichte d. k. bayer. Akad. d. Wissensch. zu München. **17**:179, 1887.

the substances was determined. Hydrochloric acid was toxic to mammals in 1:10,000, a figure markedly different from those previously reported. Chlorin poisoning was followed by a narcotic effect.

Grossmann[23] noted the appearance of lung edema following muscarin injection. Curarized dogs were used. Lung capacity, venous, carotid, pulmonary artery and left auricle pressures were recorded. He gives credit to von Basch for observing this type of edema first. After muscarin injection he claimed that there was a rise in venous pressure, right auricle pressure and left auricle pressure, and a fall in aortic pressure. Atropin administration and accelerator stimulation was followed by a disappearance of the muscarin induced lung edema. The blood flows slowly through the lung capillaries and under a high pressure. Section of the splanchnics or cervical cord did not prevent lung edema occasioned by muscarin. Strychnin was ineffective. Decreasing the amount of blood from the right ventricle prevented the appearance of the edema. Intravenous (jugular) injection of physiologic sodium chlorid solution caused signs of edema to disappear. Muscarin produced a decrease in the size of the left ventricle, and an increase in size of the right ventricle. Vagal stimulation dilated both ventricles. Muscarin probably produces a spasm of the left ventricle. Grossmann obtained stasis edema in eighty-five dogs with intact cardiac valves and strong pulses.

Grossmann, von Zeissl (vide infra) and Winkler (vide infra) are pupils of von Basch who claimed that (a) increased lung volume and (b) diminished expansibility of the lungs followed after increased filling of the lung vessels. They used special apparatus to record lung volume changes. The von Basch theory, if not discredited, at least is not accepted at present.[24] His pupils go a step further in postulating the occurrence of lung edema if (a) and (b) persisted as shown in their tracing without verification very often of the presence of an edema by direct examination of the tissues.

Sahli,[25] in a polemic against Grossmann, reiterates his criticism of Welch as the proponent of the left ventricle weakness theory of lung edema which Grossmann supports, in the main. He states also that spasm of the left ventricle and low blood pressure should be accompanied by signs of arterial anemia. Of course, clinically they are not. Therefore, Grossmann's low blood pressure data and other factors are at variance with clinical facts. The von Basch theory is completely thrown out of court. Sahli says that he obtained high pulmonary

23. Grossmann: A Study of Acute General Lung Edema. Muscarin lung edema, Ztschr. f. klin. Med. **12**:559, 1887.

24. Heinz: Handb. d. Experimentellen Pathologie und Pharmakologie **2**: 514, 1906.

25. Sahli: Pathologic Lung Edema, Ztschr. f. klin. Med. **13**:482, 1888.

artery pressures for hours and still got no edema, therefore he doubts whether Grossmann could get any edema during a short period of high pressure.

Grossmann[26] describes the microscopic and gross changes in the lungs of cases of muscarin edema. The carotid pressure served as an index of what was occurring in the pulmonary artery. He dilates further on the von Basch theory that a more than normal filling of the blood vessels is followed by an increase in the alveolar space. He does not believe that muscarin narrows the bronchioles. The intrapulmonic air space decreases before there is cardiac slowing; then it increases. With carotid bleeding, the diminished expansibility of the lungs is reduced. In one series he put physiologic sodium chlorid solution into the trachea, as much as 600 c.c. in one experiment, without changing the lung capacity. He answers Sahli by saying that lung edema can be produced in dogs by compression of the left ventricles.

Grossmann[27] later returned to the von Basch theory with a study of obturation of the right auricle and left ventricle.

Löwit[28] criticizes Grossmann for postulating pulmonary artery pressure from carotid pressure when neither Knoll nor Löwit find constant effects in the pulmonary artery pressure by asphyxiation or aortic compression. Cats and rabbits were used after receiving hirudin. Marked compression of the aorta can produce simultaneous pressure rises in the pulmonary artery or in the left ventricle, or in one alone, or no rise at all. Therefore, the condition of the pulmonary artery pressure cannot be postulated from an examination of the left auricle pressure. He criticizes Grossmann's method of diagnosing lung edema. The best test is the transudate. Compression of the aortic root also produces varying results. Narrowing the tricuspid lumen to one third of the original opening hinders the outflow of blood to the right heart, resulting in a fall in pulmonary artery pressure. A large amount of blood can be accommodated by the pulmonary circuit without producing edema. Salt injection in the jugular, plus aortic root clamping, always resulted in lung edema. With an obstructed outflow of pulmonary blood, and an increased inflow of pulmonary blood lasting for some time, a stasis edema results in curarized or noncurarized animal, although sooner in the latter. He agrees with Mayer as to the importance of accessory factors. Marked compression of the left ventricle resulted in edema only when the pulmonary artery pressure rose;

26. Grossmann: Acute General Edema, Ztschr. f. klin. Med. **16**:161, 183, 270, 310, 1889.

27. Grossmann: Lungenschwelling u. Lungenstarrheit, Ztschr. f. klin. Med. **20**:397, 1892.

28. Löwit: Ueber die Entstehung des Lungenödems, Beitr. z. Path. anat. u. z. allg. Path. **14**:401, 1893.

therefore, he disclaims left ventricle weakening as the cause. He maintains that Welch obtained his edema following asphyxia. He has often noted no volume increase in lungs with edema, and often marked volume increase in lungs after muscarin with no lung edema. Double vagotomy results in inflammatory edema after from one to two hours, because Knoll showed that vagotomy produces no change in the small circulation. The pressure changes are negative.

Toxic lung edema was next considered by him. His studies with muscarin led to different results than Grossmann's. The pulmonary artery pressure rises, while the left auricle pressure rise is only temporary and coincident with the cardiac slowing. Löwit never got a lung edema with muscarin. Intravenous injection of acetic ether produced lung edema and transudation in other parts of the body. Löwit postulates vascular wall changes. Sulphuric and butyric ether act similarly. These types resemble the following in man: (1) Acute general edema; (2) inflammatory; (3) agonal, and (4) direct irritants of the lungs. Lung edema can be produced experimentally by excessive artificial ventilation. This is not accompanied by any pressure changes as a rule, therefore, it is not of stasis origin. Von Kahldeen (1895) abstracted his article.

Alexandrow,[29] in the main, confirms Welch, but in addition introduces nerve section and infusion experiments. Vagotomy is followed by edema. Lung capacity is lessened when there is blood stasis in the lung vessels. Artificial respiration delays the onset of lung edema. Section of recurrent nerves and accessories, or section plus hindrance to ingoing air is followed by lung edema. He worked with dogs, cats and rabbits.

Von Zeissl[30] produced lung edema in dogs by intravenous injections of iodin solution. He follows von Basch in his interpretations, and gets practically the same changes as Grossmann does with muscarin. In one experiment the lung edema was accompanied by a fall in the left auricle pressure. Morphinized and nonmorphinized animals were used with thorax both intact and open.

Jacobj [31] discusses the technic of perfusing surviving lungs while under artificial respiration. The onset of edema is earlier the more dilute the blood is made. In these isolated lungs, with edema present, he hypothecates a disturbance of the gas exchange mechanism.

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29. Alexandrow: Ueber Die Entstehungsweise des Stauungsödems in den Lungen, Diss. Moskau, 1892; Abstr. Centralbl. f. allg. Path. u. path. Anat. **4**: 691, 1893.

30. Zeissl: Ueber Toxisches Lungenödem, Centralbl. f. Physiol. **7**:702, 1893; Ztschr. f. klin. Med. **27**:363, 1895.

31. Jacobj, C: Ein Beitrag zur Technik der Künstlichen Durchblutung überlebender Organe, Arch. f. Exp. Path. u. Pharm. **36**:530, 1895.

Grossmann[32] returns to the further elucidation of the von Basch idea. He claims that pulmonary artery pressure and left auricle pressure need not be registered simultaneously. Obturation of the left auricle produces a fall in carotid and venous pressures, accompanied by a marked rise in pulmonary artery pressure. The fall in venous pressure is interpreted as being due to the diminished amount of blood coming to the right heart. In this set of experiments Grossmann postulates that swelling of the lungs and their diminished expansibility is an invariable accompaniment of increased lung artery pressure, on the basis of his previous experiments. Compression of the root of the aorta causes a fall in carotid, and a rise in pulmonary artery and left auricle pressures. Fluid injected into a pulmonary vein produces the same result. In a polemic against Löwit, he believes that Löwit had clots in the blood vessels in spite of using leech extract, and that Löwit included the pulmonary artery often on aortic compression. He states, again, that the left auricular pressure rise is not directly related to the muscarin heart slowing. This rise is caused by the left ventricle spasm, and is followed by stasis hyperemia, which, in turn, are succeeded by lung swelling and diminished expansibility.

Löwit[33] answered Grossmann's critique.

Benedicenti[34] reported the occurrence of lung edema in mammals following inhalation of 25 to 30 per cent. carbon dioxid.

Winkler,[35] in administering amyl nitrite to curarized and morphinized animals, obtained lung edema with the typical carotid fall by nitrites. He is a pupil of von Basch, and used Grossmann's methods. Tigerstedt[36] cited the work of Bradford and Dean that a carotid pressure fall is accompanied by a pulmonary artery pressure rise. Tigerstedt states that amyl nitrite weakens the left heart.

Kockel[37] incorporates Weltzel's data with his own on the effect of nitric and nitrous acids on man and animal (rabbits, mice, guinea-pigs). He cites Bauer[38] as having the same results. After gassing, there is a period of relatively good health before untoward symptoms

32. Grossmann: Stauungshyperämie in den Lungen, Ztschr. f. klin. Med. **27**:151, 1895.

33. Löwit: Polemic vs. Grossmann, Centralbl. f. allg. Path. u. path. Anat. **6**:97, 1895.

34. Benedicenti: Die Wirkung der Kohlensäure auf die Atmung, Dubois Arch., 1896.

35. Winkler: Neue beiträge zur Kentniss des Amylnitrits, Ztschr. f. klin. Med. **35**:213, 1898.

36. Tigerstedt: Ergebn. d. Physiol. **2**:581, 1903.

37. Kockel: Ueber das Verhalten des menschlichen und thierischen Organismus gegen die Dämpfe der Salpetrigen und Untersalpetersäure, Viertlj. f gericht. Med. **15**:1, 1898.

38. Bauer: Festschrift zur Feier der 50 Conf. des Vereins d. Medicinalbeamten d. Kg.-Bez., Düsseldorf, 1895.

occur. Lung edema and inflammation of the respiratory passages are the most prominent symptoms. Microscopic sections show multiple hyalin thrombi in lung vessels. The injured regions become foci for bacterial invasion. The respiratory epithelium is desquamated. The heart is weakened and this adds to the initial lung edema. The decreased gas exchange yields a third factor conducive to the production of edema. Death is by asphyxiation. There is a direct local effect on the lungs.

Kunkel[39] presents a general discussion of "gaseous" poisons, symptoms and pathology, and refers in general terms to his own experiments. He outlines the following problem as to the distribution of the gas or vapor: (1) the part bound to the tissue; (2) the portion absorbed, changed or unchanged; (3) the portion resorbed, and (4) the amount excreted again via the lungs.

Magnus[40] reviews Cohnheim and Lichtheim's work, confirms it, and cites Fleischer, Dembrowski, Dastre and Loye, and Knoll as having confirmed it. He also reports on his experiments with arsenic in producing pulmonary edema.

Fouineau's thesis[41] contains no original experimental work.

Carrion and Hallion[42] injected salt solutions of various concentrations intravenously, and noted the occurrence of acute pulmonary edema. They give no tracings or records of their experiments.

Chatin and Guinard[43] record the occurrence of lung edema after the injection of methyl salicylate.

Miecamp[44] follows Teissier, his teacher, with emphasis on theory. He presents no original work.

Chanoz and Doyon[45] showed lung edema after injecting amylsalicylic ether intraperitoneally or intravenously. Death resulted from arrest of respiration. There were convulsions.

Winterstein[46] records lung edema and increased mucosal secretions in animals after carbon dioxid inhalation.

D'Achard and Loeper[47] confirm Carrion and Hallion.

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39. Kunkel: Handb. d. Toxikologie **1**:38, 1899.
40. Magnus: Die Enstehung der Hautödeme bei experimenteller hydrämischer Plethora, Arch. f. exper. Path. u. Pharmakol. **40**:252, 1899.
41. Fouineau: De l'oedema aigu du poumon, These, Paris, 1898.
42. Carrion and Hallion: Contributions experimentale a la pathologenie des oedemes, Compt. rend. de la Soc. de Biol. **51**:156, 1899.
43. Chatin and Guinard: Recherches pharmacodynamiques sur le salicylate de methyle, Ibid., **52**:669, 1900.
44. Miecamp: Pathogenie de l'oedeme aigue du poumon, These, Lyon, 1900.
45. Chanoz and Doyon: Compt. rend. Soc. de Biol. **52**:716, 1900.
46. Winterstein: Engelmann's Arch., Suppl., 1900.
47. D'Achard and Loeper: Sur la retention des chlorures dans les tissus au cours de certains etats morbides, Compt. rend. Soc. de Biol. **53**:346, 1901.

Teissier and Guinard [48] used methyl salicylate to produce edema. After curarization, artificial respiration was instituted following tracheotomy. A window in the left thorax permitted them to get the pulmonary artery pressure. Compression of the aorta was negative, except for a temporary rise in pulmonary pressure and a fall in carotid pressure. Injection of methyl salicylate produced no effect or only a slight rise in the pulmonary artery pressure. Stimulation of vagi, plus the drug, produced lung edema, but edema was not marked when the heart was irregular. They also recorded left auricular pressure. There is no need, they say, to produce a rise in the latter pressure in order to get lung edema. The left auricle pressure does not change at all after the drug is injected, while the carotid pressure gradually falls. They propose a mixed theory. First, mechanical difficulties are of themselves insufficient; second, nervous effects, such as vasodilation, plus the first, facilitate an occurrence of lung edema, but third, an intoxication is necessary to produce an edema.

Bouchard and Claude[49] confirm Josue[50] (not known to me) on the production of lung edema after intravenous epinephrin injections in rabbits. They performed six experiments, and show no records of pressure changes.

Berge[51] noted repeated pulmonary edema crises following subcutaneous injection of physiologic sodium chlorid solution in an arteriosclerotic individual who was afflicted with Bright's disease and an aortic insufficiency. There was no cutaneous edema at any time. Death occurred some time later in uremic coma with Cheyne-Stokes respiration.

Hamburger,[52] took the ascitic fluid from a patient, aged 9 years, and injected it into a calf. There was a marked increase in the lymph flow. On heating the fluid two hours at 56 C. this lymphagogic action was destroyed. The micrococci isolated from the fluid also had a lymphagogic action. Fluid flowed from the nose of the calf, and there was an hydropic swelling of the interstitial tissue of the lung. He cites the presence of lymphagogues in cases of cardiac dropsy (Lepine), inflammatory hydrops (Talma), uremics (Starling), and in chronic hemorrhagic nephritics with edema. His view is that with hindrance of outflow of blood certain products accumulate in the capillaries and

48. Teissier and Guinard: Nouvelles recherches experiment. sur la pathogen. de l'oedeme aigu du poumon., J. de Physiol. et de path. gener. **3**:42, 1901.

49. Bouchard and Claude: Recherches exp. sur l'adrenaline, Compt. rend. de seances de l'Acad. D. S. **135**:928, 1902.

50. Josue: Not located.

51. Berge: Oedeme pulmonaire provoque par l'injection souscutanee de serum artificiel, Bull. et Mem. de la Soc. méd. d. hôp. de Par., 3d Series **20**:1349, 1903.

52. Hamburger: Osmotischer Druck und Ionenlehre **2**:67, 1904.

stimulate the capillary endothelium to greater lymph production. He speaks of autogenous lymphagogues. The vessel walls may also have an increased permeability.

Meltzer[53] observed pulmonary edema in rabbits after a large dose of epinephrin. The left ventricle cannot force out all of its blood because the systemic vessels are constricted. The right ventricle, stimulated by the epinephrin, unloads with increased energy the blood which the contracting vessels drove into it. The combination produces lung edema.

Welch,[54] at Meltzer's request, restates his views on lung edema, twenty-five years after his original contribution. Welch reiterates that lung edema occurs following a passive hyperemia, and that the important factor is passive congestion in the pulmonary artery. This is obtained by producing "a disproportion between the working power of the left ventricle and of the right ventricle of such a character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." He maintains that Mayer, Grossmann and Löwit have confirmed his work. A weak pulse is not necessary. The relation between the forces of each ventricle is the essential thing. An edematous lung can be pale. Osmotic pressure, alterations in capillary endothelium and interference with lymph absorption are conceivably not sufficient factors alone to be primary causes of acute general edema of the lungs. He agrees with Sahli in that "a larger number of cases of pulmonary edema are referable to inflammatory changes in the vascular walls than is generally supposed." His opinion is based on systematic bacteriologic examinations at the Johns Hopkins Hospital necropsies.

Sahli,[55] also at Meltzer's request, still states that Welch's theory is untenable, and underscores the inflammatory type as the main one met in practice.

Jores[56] produced lung edema in four minutes in one lobe of a dog's lung by letting that lobe inhale carbonic acid through a tube. The localized effect rules out circulatory disturbance due to the heart. He quotes Mares as saying that the edema is not due to the acid but to the mechanical asphyxia which disturbs the vessel walls. A tube without gas in it produces the same effect. If a large tube is used no edema results. It is easy to obtain edema, a localized edema, if a tube is inserted into a bronchiole. Reflex respiratory standstills or ballooning a bronchus were negative. Jores concludes that the presence of an

53. Meltzer: Edema, Am. Med. **8**:195, 1904.
54. Welch: See Ref. 11; also Ref. 53.
55. Sahli: See Ref. 15; also Ref. 53.
56. Jores: Ueber experimentelles, neurotisches Lungenödem., Deutsch. Arch. f. klin. Med. **87**:389, 1906.

irritating foreign body to the mucous membrane of the smaller bronchioles is the cause of a sharply localized lung edema in a very short time. It is not a stasis edema, nor is it toxic or infectious, therefore it must be of neuropathic origin. He stimulated the external surface of the lung faradically for ten minutes. The rabbit remained quiet. Edema followed. Similar results were obtained with dogs. He believes that the electrical stimulation produces a local vasodilation. With the same technic, including section of the right vagus, done three weeks before the experiment, an edema was obtained. Section of the sympathetics and right vagus was attempted, but the animals died of pneumonia in five days. He concludes that disturbance of the gas exchange per second has no influence on the origin of lung edema.

Heinz,[57] in a general discussion of lung edema, notes its occurrence especially with cardiac poisons. The type found is an acute, general, pulmonary edema. He directs attention to the fact that lung edema may easily be simulated by excess secretion of the bronchotracheal system. Therefore, one must be cautious when making a diagnosis by a transudate emanating either from a tracheotomy opening or the mouth. He found that perfusion of a heart-lung preparation (rabbit) with a solution containing three parts Ringer's solution and one part blood usually resulted in acute, general edema in thirty minutes. Heinz also produced an epinephrin pulmonary edema. In gassing with chlorin, bromin, ammonia, hydrochloric acid, hydrobromic acid, hydrofluoric acid and nitric acid there is a preliminary expiratory standstill.

Josue and Bloch,[58] showed lung edema in rabbits after intravenous injections of epinephrin. They were confirmed by Bouchard and Claude.

Chemery[59] reviewed the subject of lung edema in his thesis, but presented no original experiments. He favors a mixed theory of lung edema causation; first, hypertension; second, chlorin retention and third, a nervous element.

Emerson[60] gave epinephrin intravenously to cats. This produced left ventricular dilatation, which is accompanied by mitral regurgitation. This in turn leads to acute congestion of the lungs, dilatation and failure of the right heart. Stagnation in the small circulation produces edema. Artificial respiration in an advanced stage of edema is of benefit.

57. Heinz: Handb. d. exper. Path. u. Pharmakol. **2**:525, 1906.

58. Josue and Bloch: Action hypertensive de la couche corticale des capsules surrenales, Semaine méd. 1907, No. 25.

59. Chemery: Contribut. a l'etude de l'oedeme aigu du poumon et de sa pathogenie en particulier, These, Paris, 1908.

60. Emerson: Artificial Respiration in the Treatment of Lung Edema, Arch. Int. Med. **3**:368 (March) 1909.

Miller and Matthews[61] studied the effects of nitric oxid, ammonia, illuminating gas, epinephrin and hydrocyanic acid. They also produced artificial mitral stenosis. Dogs and rabbits were given ether under artificial respiration. Carotid and pulmonary artery pressures were taken. Edema was obtained with nitric oxid. Both pressures fell. Irritation of the epithelium or underlying vessels is the important factor. Ammonia vapor produced the same results as nitric oxid. Carbon monoxid produced no pulmonary edema. A slight fall in carotid pressure was accompanied by a slight rise or stationary pulmonary artery pressure. No edema was obtained with hydrocyanic acid. The lung artery pressure was unchanged or lowered gradually. Lugol's solution produced a temporary rise in the carotid, then a fall, while the pulmonary artery pressure rose. The right heart was dilated, while the left heart was unchanged. Edema was produced. They confirm Löwit's observation that acetic ether, given intravenously, results in pulmonary edema in dogs. This substance produces a temporary fall in the carotid pressure. The right heart is dilated, while the left heart never is dilated. A marked bradycardia precedes cardiac standstill. A small dose always gave a decided rise in the pulmonary artery pressure, while a large dose occasionally was negative on the latter pressure, although edema was present. They say a rise in the latter pressure occurs after the edema appears. They call attention to Silbermann's work[61a] that capillary thrombosis may readily be induced by toxic agents, and that the lung capillaries, because of small caliber and low blood pressure may be especially prone to thrombosis, which may be responsible for the rise in the pressure of the lung artery. Intravenous injections of epinephrin were negative unless the thoracic aorta was ligated. Then a marked pulmonary edema followed. Stasis results because the left ventricle is unable to empty itself completely. If a marked mitral stenosis is produced, an edema follows. Acetic ether edema is usually associated with evidence of disproportion between the two sides of the heart, but they feel that the mechanical factors are not responsible for the edema.

Bokarius[62] reviews the subject briefly, and supports Welch on the basis of pathologic diagnoses in selected clinical cases out of 1,200 submitted. He chose clearly cut cases of lung edema with cardiac weakness but not valvular disease or lung changes other than the edema.

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61. Miller and Matthews: A Study of the Mechanical Factors in Experimental Acute Pulmonary Edema, Arch. Int. Med. **4**:356 (Sept.) 1909.

61a. Silbermann: Virchows Arch. **117**:288, 1889.

62. Bokarius: Zur Entstehung des Lungenödems, Viertelj. f. g. Med. **41**: 307, 1911.

Knowlton and Starling,[63] in revising the technic of the isolated mammalian heart-lung preparation method, eliminate the mercury because enough of it is taken up by the perfusion fluid to have a deleterious effect. The lung capillaries suffer first, and after a somewhat variable period pulmonary edema usually terminates the experiment. With this defect corrected, they noted that when the point of maximum cardiac output is reached the venous pressure rises rapidly, and that if it is maintained pulmonary edema always appears.

Klemensiewicz[64] noted that with fresh serum no edema occurs in the isolated heart-lung preparation. If old serum, or too dilute serum, or isotonic solutions are used, then lung edema occurs easily, whether the lungs are artificially respired or not. Ligation of vessels at the hilus injures the vessels, and on release of the ligature edema sets in regularly (rabbit).

Kotowschtschikow[65] reviews lung edema in a very able manner. He performed about seventy-seven experiments on dogs. They were given morphin and chloroform. If an open thorax operation was performed, curare was given. He obturated the heart chambers; infused; ligated the aorta; and sent emboli into the lung capillaries. Obturation of the left auricle was the most successful procedure in producing edema. The pulmonary artery pressure rose, the carotid pressure fell, the pulse remained about constant, while the right ventricular pressure rose markedly. A lycopodium seed suspension as emboli produced edema in two experiments. A marked hydremia usually produced edema. Hindrance of pulmonary outflow is essential. Silver nitrate was given in thirty-six experiments. Thirty-four of the animals showed lung edema. These could be divided into two groups: First, those in which mechanical factors helped produce stasis; second, those in which no such factors appeared. In most cases, the right ventricular pressure rose, the left auricular and aortic pressures fell. There was usually asynergy of the cardiac chambers, with the left heart weaker. Ether injection produced lung edema. No mechanical changes appeared; therefore vessel wall injury is hypothecated by the author. Methyl salicylate produced lung edema in each of six experiments. The right ventricular pressure can be high but need not be. There is no change in the carotid pressure. Muscarin produced no changes. Lugol's solution was used, but the author does not draw any conclu-

63. Knowlton and Starling: Temperature and Blood Pressure Variations on Isolated Mammalian Heart-Lung Preparation, J. Physiol. **44**:207, 1912.

64. Klemensiewicz: Das Lungenödem, Krehl and Marchand's Handb. d. Allg. Pathologie, Part 1 **2**:424, 1912.

65. Kotowschtschikow: Zur Frage nach den Veränderungen der Herzthätigkeit und des Blutkreislaufs bei acutem Lungenödem, Ztschr. f. exper. Path. u. Therap. **13**:400, 1913.

sions from a few experiments. He attempted to confirm Jores, but was unable to do so. He believes that the most common cause of lung edema is a toxic one, and that less often mechanical factors are operative. In the latter cases the pulmonary artery pressure is higher, the right ventricle works better and the systemic blood pressure is lower. The mechanism of toxic edema experimentally induced may be increased permeability of the lung capillary walls, or capillary thrombosis.

Biedl[66] notes that an intravenous lethal dose of epinephrin causes a lung edema in rabbits which is a stasis edema.

Kraus[67] performed his experiments on intact rabbits and on cats with open thorax. The latter had their lung volume, pulmonary artery, venous and carotid pressures recorded. Urethane was given, but no morphin. The roentgen ray shows a larger heart after salt is injected intravenously in rabbits. The carotid pressure rises, the lung volume increases, then decreases. A second injection produces no increase in the size of the heart. Injection of salt solution plus double vagotomy produced an acute pulmonary edema immediately. This occurs in cats and rabbits, whether the thorax is open or not. Epinephrin aids the onset. His electrocardiographic findings are recorded elsewhere, he says, in a journal not stated. He interprets the roentgenograms as showing a diminished air capacity and hyperemia in the edematous lungs.

Evans and Starling[68] used a method in their isolated heart-lung preparations which diminished the tendency for pulmonary edema occurring so often. After some hours there is always more or less edema. Führer and Starling,[69] using the same method, showed that with a rise in venous pressure, the heart volume increases, and there is a rise in the lung artery, left auricle and aortic pressures. On the other hand, the venous pressure shows only small differences during wide alterations in the aortic pressure. If the left ventricle fails, and the right heart beats strongly, then the pulmonary pressure rises. Patterson and Starling[70] state that accumulation of blood in the right heart, with fair response of the latter, may cause pulmonary edema. Maximum cardiac efficiency, persisted in too long, tends to give rise to pulmonary edema. Patterson, Piper and Starling[71] conclude that within wide limits cardiac output is determined by and equal to the

66. Biedl: Innere Sekretion, Berlin, Ed. 2, **1**:522, 1913.
67. Kraus: Ueber Lungenödem., Ztschr. f. exper. Path. u. Therap. **14**: 402, 1913.
68. Evans and Starling: Oxidation in Lungs and Isolated Heart-Lung Preparation, J. Physiol. **46**:415, 1913.
69. Führer and Starling: Pulmonary Circulation, J. Physiol. **47**:290, 1913.
70. Patterson and Starling: J. Physiol. **48**:357, 1914.
71. Patterson, Piper and Starling: J. Physiol. **48**:497, 1914.

inflow into the right auricle. A heart weighing 50 gm. puts out as much blood as it receives, whether this be 200 c.c. or 2,000 c.c. per minute.

Weber[72] criticizes Grossmann's data obtained with muscarin. Weber studied experimental asthma and innervation of the bronchial muscles. No mention is made of edema onset in his experimental lungs.

Magnus, Sorgdrager and Storm van Leeuwen[73] return to Magnus' problem of 1902, concerning the impermeability of the alveolar epithelium to ammonia gas. Höber, 1912, showed the appearance of ammonium hydroxid in the lungs, after ammonia was put into the pulmonary artery, and when pulmonary edema was present. Magnus[74] never obtained lung edema when ammonia was put into the circulation. Magnus et al repeated and confirmed Magnus' 1902 experiments. They showed that with ammonia inhalation the greatest absorption and injury takes place via the tracheal and bronchial mucous membranes, and that the alveolar epithelium is relatively impermeable in rabbits even with ammonia percentages of 5.8 to 8.5. They also used the isolated lung preparation (Brodie's method). Cats and rabbits were etherized. An arterial pressure of from 35 to 38 mm. was maintained. No lung edema appeared in normal lungs during the duration of the experiments — three hours. In eleven experiments, from 0.015 to 0.017 per cent. of ammonia was placed in the blood. The drug seeps through the pleura but does not appear in the expired air. In one experiment the lung was kept bloodless a short time, while in another chloroform had been administered and fluid appeared in the trachea. The expired air contained ammonia in both experiments. The plethysmograph showed absence of bronchial spasm. Five experiments were done with increased amounts of ammonia in the blood, from 0.027 to 0.045 per cent. Lung edema followed and ammonia appeared in the expired air. Therefore, they say, the alveolar epithelium is injured. With the onset of lung edema, the respiratory excursions become smaller and finally stop. The normal alveolar epithelium is impermeable to ammonia, while that of the pathologic lung is not. McGuigan's paper[75] contains references on ammonia absorption by the lungs. A few of the experiments that he cites seem to have caused pulmonary edema.

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72. Weber: Experimental Asthma and Innervation of the Bronchial Muscles, Arch. f. Anat. u. Physiol., 1914, p. 63.

73. Magnus, Sorgdrager, and Storm van Leeuwen: Ueber die Undurchgängigkeit der Lunge für Ammoniak, Arch. f. g. Physiol. **155**:275, 1914.

74. Magnus: Schmiedeburg's Arch. **48**:100, 1902.

75. McGuigan: The Absorption and Excretion of Ammonia by the Lungs, J. Pharm. & Exper. Therap. **4**:453, 1913.

Modrakowski[76] is the first investigator of experimental lung edema per se in surviving mammalian lungs. He employed the Brodie apparatus. More than fifty cat preparations were perfused with defibrinated blood or physiologic sodium chlorid solution containing from two thirds to three fourths defibrinated blood. He postulated the presence of edema when the following combination was present: a transudate in the trachea, no maximal pulmonary expansion, and when the lung did not readily collapse. He produced an acute lung edema in five minutes, and thereupon the experiment was stopped at once. In his first series, the pulmonary artery pressure was raised above normal, and considerably above, while the venous outflow was unhindered. Edema did not occur in this series. In the second series, the lung outflow was hindered by raising the pulmonary vein pressure. Lung edema was produced when the pulmonary artery and pulmonary vein pressures were raised high enough. Venous stasis alone, with venous pressure below 35 mm., is negative. Lung edema arises when with a pulmonary artery pressure of not less than 35 mm. Hg the venous outflow is so obstructed that their difference drops to 8 mm. If the epithelium or vessel walls are injured, then the permeability of the lung tissue becomes greater. In a hepatized lung (right lower) with the other lobes postpneumonic, edema was produced by only increasing the pulmonary artery pressure. In this experiment there was no venous stasis present. Ammonia in the blood produces edema with either normal or high pulmonary artery pressure, and when there is no obstruction to pulmonary vein outflow.

Staehelin[77] reported seeing many cases of phosgene poisoning all of which showed a general bronchitis and bronchiolitis with lung edema. Fever was present in all the cases. Microscopic examination of one case gave the following data—inflammation of bronchi, marked desquamation of alveolar epithelium, numerous alveoli filled with fluid, and thrombi in many pulmonary arterioles. He believes that there need be no assumption of bacterial invasion to explain the phosgene effects. Hydrochloric acid arises from carbonyl chlorid in a moist environment, and injures the epithelium.

Roos[78] presents five cases of phosgene poisoning, some covering a period of six years, with detailed description of signs, diagnosis, treatment and postmortem examination. This report is unique in that a real attempt was made to centralize attention on cause and result. At venesection it was noticed that the blood coagulated very quickly. Notable observations by Roos are the decreased cardiac energy in all

76. Modrakowski: Experimental Lung Edema in Surviving Mammalian Lungs, Arch. f. d. g. Physiol. **158**:527, 1914.
77. Staehelin: Contrib. Ed. Handb. d. Inn. Med. **2**:287, 302, 315, 1914.
78. Roos: Phosgenvergiftungen, Thesis in Viertelj. f. ger Med. **47**:67, 1914.

the cases, the lung changes, the heart picture and the negative spectroscopic and chemical examinations of the blood. The roentgenogram showed cardiac dilatation in two cases. Summarizing his data, we have acute dilatation; severe cough; after a few hours marked dyspnea, nearly asphyxial; albuminuria; stasis polycythemia and a marked leukocytosis; pneumonic foci, with desquamation of alveolar epithelium and leukocytic infiltration; subpleural petechial hemorrhages; acute bronchiolitis; multiple thrombi of lung arteries; increase in the amount of fibrin and multiple thrombi in brain, lungs and intestinal vessels.

Kuno[79] studied the dog's heart-lung preparation. The pressure in the left auricle rises steadily with increase in venous inflow. The pulmonary artery pressure always rises when there is increase in the venous inflow beyond a certain point.

Evans and Matsuoka[80] deduct from their isolated heart-lung preparation experiments, that lung edema comes on with ease at high pressures (apparently above 170 mm.) in the aorta. Knowlton and Starling[81] state that increase in cardiac output runs parallel with increased aortic pressure until a maximum output is reached. Then the output falls rapidly. The venous pressure rises before there is any falling off in total output of the heart. Markwalder and Starling[82] find that the cardiac output is markedly independent of other factors. The previous data did not consider the coronary circulation, they insist.

Matsuoka[83] discusses the pathology of obstructive lung edema as obtained in the Starling heart-lung preparation. His English is ambiguous, and there seem to be too many conclusions for the amount of data presented. Defibrinated blood with leech extract was the perfusing fluid used. The cardiac output was taken as a measure of venous inflow. When there is a relatively low arterial pressure, a very large venous inflow must be maintained for some time to produce edema. It is possible to increase the venous inflow without causing edema when a high arterial pressure prevails. Obstruction of the aortic root produces an edema with a relatively small venous inflow. The pulmonary artery pressure is raised in such a case. The blood pressure in the pulmonary artery rises with a coordinate rise of the inferior vena cava. During edema, the heart output may be reduced to a minimum, the blood content of the heart may be increased to a maximum, the pressures of the pulmonary artery, inferior vena cava, and right auricle may be increased to a maximum, all quite indepen-

79. Kuno: Pulmonary Circulation, J. Physiol. **50**:140, 1915.
80. Evans and Matsuoka: Gaseous Metabolism and Efficiency of the Mammalian Heart, J. Physiol. **49**:378, 1915.
81. Knowlton and Starling: J. Physiol. **44**:206, 1912.
82. Markwalder and Starling: J. Physiol. **48**:348, 1914.
83. Matsuoka: Pathology of Obstructive Edema of the Lung. Heart-Lung Preparation, J. Path. & Bact. **20**:53, 1915.

dently of the height of arterial pressure and amount of venous inflow. With a heart weighing 45 gm. the pulmonary artery pressure must be over 40 mm. Hg and be accompanied by venous obstruction so that lung edema may arise. Edema never occurs in healthy dogs' lungs when the pulmonary artery pressure is lower than 40 mm. Hg. The principal factors in transudation are the high pressure in the pulmonary circuit and the excessive passive dilatation of the lung capillaries. The gaseous metabolism and the energy consumption of the heart decrease in obstructive lung edema. The heart always dilates before the occurrence of edema.

Martin Fischer[84] discusses lung edema briefly in his thesis, and mentions a few experiments of his own. An edema results whenever the oxygen supply to the lung parenchyma is interfered with sufficiently. This can be done effectively by ligation of nutrient vessels, directly or indirectly, via interference in the systemic circulation, such as compression of left ventricle or aortic root. Ligations to a point immediately below the subclavian artery lead to edema, because the bronchial arteries leave the aorta just below the left subclavian. Ligation below the bronchial arteries is negative. The lack of oxygen leads to accumulation of acids in the tissues. Clinically, pulmonary edema occurs more frequently in nephritis than in heart disease because toxic bodies injure the lung parenchyma as well as other tissue. It is easy to produce edema in the excised lung because there is an interference with the normal oxygen supply. Fisher took sheep's lungs and permitted water or M/6 (0.975 per cent.) sodium chlorid solution to trickle into the pulmonary arteries, producing an intense edema. A lung weighing 500 gm. will take up several liters in an hour. Two periods can be designated. During the first period there is no fluid in the trachea. Later, the pleural surface is moist, and a bloody, frothy fluid emerges from the trachea. Although the veins are not ligated, no fluid emerges. The longer the lungs have been out of the animal the more quickly do these signs of pulmonary edema appear. Sodium citrate and sodium sulphate are more effective than sodium chlorid. In other words, the salts which dehydrate various protein colloids best are most effective, and therefore, the colloid theory of water absorption applies here. More water is held because acids are produced in the tissues. The tissue colloids have their capacity for water increased by the acids present.

Schäfer[85] gives an excellent report on chlorin gas poisoning. He commends Lehmann's work. Cats, rabbits and dogs were anesthetized, and then gassed. Ringer's solution saturated with chlorin injected

84. Fischer: Edema and Nephritis, Ed. 2, 1915, p. 233.
85. Schäfer: On the Immediate Effects of the Inhalation of Chlorin Gas, Brit. M. J. 2:245, 1915.

intravenously produced a slight fall in blood pressure and a slight increase in the depth of respiration. Inhalation (1 per cent. chlorin) had no immediate special effect on blood pressure or respiration, but ultimately the blood pressure fell, the respirations became deep and convulsive prior to complete arrest, and the pulse was slowed. Substitution of air produced recovery with higher blood pressure. The chlorin cannot be carried to the tissues in a free state. The short exposures show changes only in the lungs. They are congested, more solid and are slightly crepitant. He believes that fatality may be due to obstruction of pulmonary vessels. Experiments with surviving lungs and with lungs in the intact animal show a bronchiolar dilatation during gassing. This was done by catching the air escaping from the lung surface through needle holes. Chlorinated Ringer's solution perfused into the pulmonary artery produces marked constriction. Schäfer presents microscopic plates of edema, interstitial and alveolar, and of capillary engorgement. Presumably, the edema is secondary to the vascular obstruction. Mucus does not play an important part (excluded by atropin). Bromin vapor is less deleterious.

Hill[86] discusses gas poisoning especially with chlorin. The respiratory epithelium and pulmonary capillaries are injured, and the osmotic pressure of the damaged tissue is raised, producing the edema. Albuminuria is conceivably due to decreased oxygen supply to the kidney. Barcroft, he says, has shown the presence of an increased acidity of the blood. The edematous fluid produced may drown the animal. In weak concentrations, chlorin does not produce death by stasis in pulmonary vessels. When lungs were artificially respired and manipulated so that a chlorin-air mixture could be sent into one lung leaving the other airless, then an edema arose in the first lung, followed by asphyxia and failure of circulation. Recovery was rapid if air was sent into the normal lung. Kuno and Hill, he reports, administered chlorin in heart-lung preparations. They obtained congestion and edema, while the blood became more and more venous. The cardiac output was diminished. A microscopic description is given. Strong concentrations of chlorin gas causes contraction of the bronchiolar musculature. Pneumonia and bronchitis are almost invariable sequels.

Matsuoka[87] believes that the lung edema of beri beri is a characteristic feature of the disease, and is essentially an obstructive edema. This citation is of value in that Yamagiva, the noted pathologist, says that this lung edema is due to the contraction of pulmonary arterioles and bronchioles.

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86. Hill: Gas Poisoning, Brit. M. J. **2**:801, 1915.
87. Matsuoka: Lung Edema in Beriberi, J. Path. & Bact. **20**:191, 1916.

Slovtzov, Chernewski and Xenophontov,[88] in a study on the chlorin content of the air as affecting oxidative functions and gaseous exchange, state that there is a diminished oxidation lasting for some hours.

Slovtzov[89] finds that in rabbits chlorin inhalation increases the coagulation time, diminishes the alkalinity, destroys the leukocytes, increases the red blood corpuscles, and increases the thrombin content in pulmonary tissue.

Slovtzov[90] describes the clinical signs, pathology and physical findings in cases of phosgene poisoning in man, horses, guinea-pigs, rats and dogs. The acute poisoning resembles that induced by chlorin, although it is milder. Most noticeable are the lung changes, myocarditis, nervous depression and alterations in the blood. The red cells are disrupted, there is increased coagulation and viscosity and decreased alkalinity.

Lucherini[91] gives a graphic account of gas poisoning from the war zone.

Auer and Gates[92] continue their study of fulminant pulmonary edema induced by intratracheal administration of epinephrin. They had previously found the onset more rapid in the vagotomized rabbit. Intratracheal administration of epinephrin in this series of rabbits gave them the following results: In twenty-seven experiments, marked edema occurred in twenty-one with vagi cut. In sixteen with vagi intact, slight edema was present. Direct observation (six out of seven experiments) of the heart showed that epinephrin induced alternating strong and weak beats of the left ventricle with halving of its rate. The dilatation of the left auricle was often tremendous. Artificial respiration has a restraining influence on the onset of lung edema. Tracheal stenosis facilitates edema production. Atropin exerts a protective action. Auer and Gates favor Welch's view of the disproportionate activity of the ventricles which in their experiments is induced by adrenalin.

Kuno[93] observes that when the blood used for the heart-lung preparation (dogs) is somewhat old, then the lungs gradually pass into an edematous condition. Postulating that the pulmonary circulation in

88. Slovtzov, Chernewski and Xenophontov: Chlorin on Oxidative Functions and Gas Exchange, Vratschebnaya Gaz., 1916, p. 23; also Physiol. Abstr. **2**: 621, 1917.

89. Slovtzov: Chlorin on Animals, Arch. d. Sc. Veterinaires, 1916, p. 3; also Physiol. Abstr. **2**:621, 1917.

90. Slovtzov: Phosgene Poisoning, Russk. Vrach **15**:649, 1916.

91. Lucherini: Asphyxiating Gases, Arch. farm. sper. **22**:429, 1916; also Chem. Abstr. **11**:995, 1917.

92. Auer and Gates: Adrenalin Pulmonary Edema, J. Exper. M. **26**:201, 1917; Ibid. **23**:755, 1916.

93. Kuno: Amount of Blood in the Lungs, J Physiol. **51**:154, 1917.

edema is very slow, he kept the venous supply to the heart very low in two experiments in which he determined the amount of blood present in the lungs in edema. In normal lungs, the blood was from 8.8 to 19.4 per cent. of the total blood (equal to 7 per cent. of body weight), depending on the velocity of the blood. The edematous lungs contained 23.4 and 26.2 per cent. of the total blood.

Pellegrino[94] reports histologic researches on the pulmonary alterations following inhalation of bromin.

Kramer[95] describes the effect of chlorin on the lungs, noting among other things thrombosis in lung and heart vessels.

Klotz[96] describes acute death from chlorin poisoning in mice, guinea-pigs and rabbits. Concentrations of from 1:1,000 to 1:10,000 are lethal in from three minutes to one half hour usually. A postmortem examination shows hyperemic lungs, with little fluid blood in congested areas. The blood coagulates within the dilated pulmonary capillaries. The unusually rapid coagulation may be the result of the intense edema whereby the blood constituents within the vessels are greatly altered. Human blood in 1:1,000 concentration coagulates in fifteen seconds, while stronger concentrations reduce this time. Hake[97] found that diluted blood yielded a colorless filtrate after chlorin gas was bubbled through it. A practically colorless precipitate was formed at the same time. The iron found gave the tests for the ferric salts.

Kruglevsky, Boldereff, Neporsky, Neiding, Sereisky and Gokh[98] present a series of papers on acute edema produced in gas poisoning. They discuss treatment, effect on vegetative nervous system, nervous symptoms, psychic symptoms and the intravenous oxygen treatment.

Meek[99] produced lung edema by intravenous injection of collargol. The fluid practically poured from the trachea. A microscopic study showed that it was purely an obstructive edema, with emboli in the pulmonary and coronary circulations.

General treatises on lung edema of importance are those by Ziegler,[100] Staehelin,[77] Heinz,[57] Kunkel[39] and Klemensiewicz.[64]

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94. Pellegrino: Histological Researches on the Pulmonary Alterations Following the Inhalation of Bromine, Arch. farm. sper. **24**:58, 1917.

95. Kramer: Chlorin Poisoning, Viertelj. f. ger Med. **53**:181, 1917; also Chem. Abstr. **12**: 1918; also Physiol. Abstr. **2**:528, 1917.

96. Klotz: Acute Death from Chlorin Poisoning, J. Lab. & Clin. Med. **2**:889, 1917.

97. Hake: Chlorin on the Blood, Lancet **2**:86, 1915.

98. Kruglevsky, Boldereff, Neporsky, Neiding, Sereisky and Gokh: Acute Edema of the Lungs and Various Phases of Gas Poisoning, Russk. Vrach **16**: 385, 1917; also Physiol. Abstr. **3**:61, 1918.

99. Meek: Personal Communication, 1918.

100. Ziegler: Lehrb. d. allg. Path. **2**:765, 1906.

Cushny[101] notes the frequent occurrence of lung edema in cats and rabbits after poisoning with pilocarpin. This has also occurred in man. Pilocarpin, in toxic amounts, contracts the bronchi, retarding the movement of the air, retards the heart, slowing the circulation through the lungs, and has a tendency to cause convulsive movements, accompanied by rapid and labored respiration, which eventually becomes slow and weak. Asphyxia follows.

STATUS OF THE PROBLEM AFTER NOVEMBER, 1918

Shortly after the armistice was signed November 11, permission to various war department groups of investigators was granted allowing them to publish their observations on experimentally induced conditions in which pulmonary edema occurred as a prominent symptom. However, there has as yet been no comprehensive experimental study submitted concerning the cause and treatment of the edema. Barbour and Williams[102] report the effects of chlorin on isolated bronchi and pulmonary vessels. Winternitz and Lambert[103] discuss the pathology of lungs obtained from gassed dogs, with emphasis on the edema as a cause of death. Underhill[104] delivered an excellent Harvey lecture on the physiology and experimental treatment of poisoning with the lethal war gases in which considerable experimental data were summarized, but the data were not submitted.

SUGGESTIVE METHODS FOR THE STUDY OF EXPERIMENTAL LUNG EDEMA

The detailed investigation of lung edema caused by toxic gases in the medical section of the Chemical Warfare Service directed the attention of the group at the University of Wisconsin Medical School laboratories to the following points in relation to the onset and cause of the edema. Whether there is an increase or decrease or both in (1) the blood volume, (2) red and white cell count,(3) hemoglobin percentage, (4) amount of fibrin, (5) thrombin, (6) freezing point of blood, (7) presence of lymphagogues in the blood stream, (8) spectroscopic examination of the blood, (9) chemical examination of the blood, (10) agglutination, (11) viscosity of the blood, (12) coagulation time, (13) blood counts from the right and left hearts, (14) the alkali reserve, (15) the p_H value of the blood, (16) histologic changes

101. Cushny: Textbook on Pharmacology, 1918.

102. Barbour and Williams: The Effects of Chlorin on Isolated Bronchi and Pulmonary Vessels, J. Pharmacol. & Exper. Therap. **14**:47, 1919.

103. Winternitz and Lambert: Edema of the Lungs as a Cause of Death, J. Exper. M. **29**:537, 1919.

104. Underhill: The Physiology and Experimental Treatment of Poisoning with the Lethal War Gases, Arch. Int. Med. **23**:753 (June) 1919.

in the bone marrow. In addition to these, the following topics require investigation: (17) the cause of polycythemia, whether it is due to decreased blood volume or to decreased oxygen supply; (18) roentgen-ray studies of the heart and lungs; (19) the first sign of the onset of edema, or a simultaneous factor occurring at the time of edema onset; (20) the pathology at various stages up to the time of death; (21) the vital capacity of the lungs; (22) wet and dry weights of the lungs; (23) response to increased oxygen or carbon dioxid administration, especially from time of gassing up to the onset of edema; (24) pressures in the following vessels and heart chambers — carotid, aorta, pulmonary vein, pulmonary artery, jugular vein, right ventricle, left ventricle, brachial artery; (25) wet and dry weights of tissues other than the lungs, as, for instance, muscle, to account partially for loss in blood volume; (26) direct effect of toxic substance as gas or chemical on the isolated or excised heart by perfusion; (27) direct effect on a surviving lung and such isolated pulmonary structures as arteries, veins and bronchi; (28) the cause of dyspnea; (29) the respiratory quotient; (30) the respiratory minute volume; (31) the picture produced by gassing one lung or lobe; (32) the presence of bronchiolar spasm.

Following the discovery of the cause of edema, one expects that the treatment of the condition could be followed out along suggestive leads. However, under the stress of the war situation, the study of treatment was instituted practically simultaneously with the study of the cause of toxic gas edema. These measures, briefly summarized were: the effect of (1) bleeding; (2) infusions of physiologic sodium chlorid solution, glucose, acacia and mixtures of these; (3) morphin; (4) atropin; (5) the digitalis series and other cardiac drugs; (6) oxygen—by vein, abdomen, etc., attempts at extrapulmonic respiration; (7) neutralization of chemical inhalants in the first stage of poisoning; (8) neutralization of gas products in the respiratory epithelium before injury to the cell has advanced very much; (9) possibility of regeneration of respiratory epithelium by drugs or chemicals; (10) changing the content of the blood so as to overcome the biochemic changes extravascular to the lung capillaries; (11) control of the alkali reserve; (12) maintenance of normal body temperature, etc., etc.

SUMMARY

A survey of the literature shows that the methods for production of edema fall into a few categories. The first method tried was the experimental production of pulmonary emboli by the use of fat droplets, lycopodium seeds, etc. (Virchow, Klotz). The edema resulting from pulmonary emboli may be explained in several ways. It may

arise because there is a diminished blood supply in the lung nutrient vessels via the aorta, due to the damming back of the blood, or because the right heart continues its pumping action against the emboli obstructions, increasing thereby the permeability of the turgid pulmonary capillaries. Then, again, in the diminished nutritional supply of the heart, there may result a disproportionate activity of the cardiac chambers with the left weaker than the right.

A group of methods can be gathered under the caption "Injury to Pulmonary Capillaries," either from within the vessels or from without. The blood flowing within the vessels may be altered, for example, diluted, as in Cohnheim's and Lichtheim's hydremic plethora animals, or in perfusion of isolated heart-lung preparations (Jacobj, Evans, Lovatt, etc.), a collapse in the normal permeability of the lung capillaries results, with the escape of fluid into the extracapillary space, rupturing of the alveoli, and finally filling of the air spaces. The blood may be concentrated, resulting in an anoxemia. The capillary endothelium may be injured directly with acetic ether (Löwit, Miller and Mathews) administered intravenously, or by ammonia (Magnus et al, Modrakowski). A number of French workers have attempted to produce pulmonary edema by electrical stimulation of the exposed lung and have thought that the results obtained suggested a nervous element. They insist on a reflex dilatation of the lung vessels (Jores, Teissier and Guinard). There seems to be little experimental evidence for this point of view. Another possible cause for the pulmonary injury is the production of acid products in the lung interstitial tissue due to altered blood in the nutrient vessels of the lung (Fischer).

Injury outside of the pulmonary capillaries may result from a destruction of the respiratory epithelium, as, for example, by toxic gases (Lehmann, Pettenkofer, Kockel, Roos, Modrakowski, Schäfer, Hill). Fluid would escape into the air spaces due to increased permeability of the alveolar wall resulting from the injury. Another form of injury to the respiratory epithelium might follow bronchiolitic spasm, as in chlorin gas poisoning (Barbour and Williams).

The inflammatory type of pulmonary edema, which Sahli insisted on as the chief type in man (confirmed by Welch), might be considered as a combination of intravascular and extravascular injury. Hamburger brought proof to show the lymphagogue power of certain bacteria and their products in the blood stream. Pathologic evidence also indicates that bacteria can invade the interstitial pulmonary tissue and induce an edema by altering the physicochemical conditions. It is also evident that injury of the lungs in gassed individuals results in diminished resistance to bacterial invasion.

A great mass of work has been done, initiated by Welch, in showing the onset of pulmonary edema in all conditions in which the

mechanical efficiency of the left ventricle is reduced to a greater extent than that of the right ventricle. The pressures in systemic and pulmonary vessels were recorded to prove this assumption. Welch was the first to show that injury or compression to the left ventricle was followed by a pulmonary edema. Others feel that thrombi in the left coronary artery might do this. Then, again, the toxic action on the left ventricle of rapid intravenous injections of epinephrin seems to corroborate Welch's assumption (Beidl, Auer and Gates, Meltzer, Bouchard and Claude). Probably, the cardiac disproportion is the cause of the edema of asphyxia, whether agonal or not, or, at least, it is a contributing cause. Some observers feel that the heart is the primary cause of edema in certain types of gas poisoning, indicated by its dilatation and change in venous pressure.

It is conceivable that a pulmonary edema may be the resultant of a group of causes. For example, a toxic substance might injure both lung and heart simultaneously, and as the edematous fluid finds an easy outlet, the heart may be developing an asymmetrical pumping activity and thereby massing the blood on the venous side of the lungs. Or a vicious circle might be produced. A substance might induce edema in the first place by injury to the lung parenchyma. This might result in a concentration of blood, which would in turn reduce its oxygen carrying capacity and result in a decreased efficiency of the heart due to poor nutrition. Finally, this might lead to an increase in blood in the right heart, with a greater seeping of fluid through the dilated pulmonary capillaries into the air spaces.

It would seem that the work which has been done on experimental pulmonary edema indicates that the mechanism of causation of pulmonary edema must be sought for beyond the immediately obvious cause, as, for example, intravenous emboli; intravenous injection of drugs like epinephrin and muscarin and toxic chemicals, such as acetic ether, silver nitrate, collargol, etc.; injury to the chambers of the left heart, particularly the ventricle; infusions of large amounts of fluid, with or without vagal section; electrical stimulation of lung tissue directly; inhalation of irrespirable gases and vapors (chlorin, hydrogen sulphid, hydrochloric acid, etc.); ligations and compressions of aortic and pulmonary branches; occlusion of bronchi and bronchioles; alterations in the content or amount of blood; obturation of chambers of the left heart; increasing the venous inflow; overriding the maximum cardiac output; and decreasing the oxygen supply to the lung parenchyma.

AN INVESTIGATION OF THE SIZE OF THE HEART IN SOLDIERS BY THE TELEROENTGEN METHOD*

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It is not known with sufficient accuracy whether exertion, such as soldiers undergo in warfare, is accompanied by enlargement of the heart. The present study was undertaken to obtain information on this point. The examinations were made during May, 1919, of soldiers who had seen active service in the American Expeditionary Forces.[1]

The men were selected without regard to special criteria by line officers at one of the camps in the vicinity of New York.[2] Infantrymen were chosen or men who had been subjected to an equivalent amount of privation and exertion. In this report are given the results of the study of the size of the heart only. Physical examinations were made and electrocardiograms were taken, but the results of these further studies are reserved for later communications.

The examinations now reported were roentgenographic.[3] The exposures were made with sternum turned to, and parallel with, the plate. The distance from the anticathode of the roentgen-ray tube to the photographic plate was 6 feet. A strip of lead about 10.0 cm. long, 6.0 mm. wide, and about 3.0 mm. thick was laid on the skin over the spines of the vertebrae and secured with adhesive plaster. Two acute angles of lead were similarly secured — one in the suprasternal notch and the other in the infrasternal notch. The target of the roentgen-ray tube was adjusted to the level of the lower angle. Whether correct anteroposterior alignment was obtained, could then be ascertained by examining the plate.[4] The exposures were made in

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1. At the same time similar investigations were carried on by Capt. B. Smith at U. S. General Hospital No. 9, Lakewood, N. J. The results of his examinations are given in a separate communication in this issue of the ARCHIVES OF INTERNAL MEDICINE.

2. I desire to express my thanks to Major-General Shanks, Commanding Officer of the Port of Embarkation, Hoboken, for his courtesy in placing these soldiers at my disposal.

3. I am indebted to Dr. Witherbee, who made the roentgenograms, for his painstaking cooperation.

4. Mention is made of this technical detail because the use of this method secures greater accuracy than that which employs a lead strip on the sternum and a ring over the a vertebral spine.

the standing position. In making studies of this kind, Bardeen [5] made the exposure "during deep but not forced inspiration and with two half second exposures with an intervening half second so as to insure a diastolic outline." The exposures were made by Smith [6] during an inspiration of moderate depth after the subject had taken a deep breath and expired it. A method involving deeper breathing than normal has this purpose: it frees a larger portion of the cardiac shadow from the shadows of the surrounding viscera, especially the liver, and it permits the drawing of the outline of the cardiac shadow with greater ease. It is admitted that there is a disadvantage in the procedure; when the breath is held too long it occasions too great a filling of the heart, the photograph of which is, in consequence, larger than normal. A modification of the usual technic was, therefore, introduced in this study. No directions for breathing during the exposure were given; the men breathed normally. In order that the phase of respiration in which the plate was secured might be known, the following technic was devised.

On the plate holder a lead strip was secured to indicate the neutral position of the vertically hanging lever of a Marey tambour tipped with a lead ring. The tambour was connected by rubber tubing with a Politzer bag held in position in the right axilla by a binder secured by tying its tails; metal fastenings were, of course, avoided. During respiration, the lever swung to one or other side of the neutral line indicated by the lead strip. The side to which the lever swung during expiration was indicated on the plate holder by fastening there a lead letter E. The exposures were brief, a fraction of a second, perhaps as little as one-tenth second on occasion, so that the image of the lead ring of the lever was sharp. When the exposure was longer, or the breathing faster, the trail of the lever, as it swung across the plate, appeared on the plate and showed this fact. The lever of the tambour was in view of the operator, so that by observing it the exposure could be made in any phase of breathing. The desired information was, accordingly, recorded on the plate. The attempt was made to secure the exposures during normal inspiration. This succeeded in 140 of 161 instances (I, ?, Table 1).

But to study the effect of normal breathing on the size of the heart, the heart in fifty-six instances was photographed both in inspiration and in expiration. Note should be taken of the fact that in many

5. Bardeen, C. R.: Determination of the Size of the Heart by Means of the X-Ray, Am. J. Anat. 23:423, 1918.

6. Smith, B.: Teleroentgen Measurements of the Hearts of Normal Soldiers, Arch. Int. Med., this issue, p. 522.

TABLE 1.—DATA AND MEASUREMENTS OF THE HEARTS OF THE SOLDIERS EXAMINED

No.	Phase Respiration	P.	Weight, Kg.	Height, Cm.	Age, Yrs.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Notes
1	I		53	157	21	13.4	13.4	94	38	
2	I ?	+	53	152	29	12.7	13.6	102	37	Wounded
3	I		54	164	40	12.0	13.1	108	46	
4	I	+	54	162	20	11.9	13.3	86	40	
5	I		55	158	29	12.8	14.5	122	42	
6	I	+	56	158	25	13.9	13.9	120	43	
7	I		56	173	24	13.8	15.7	112	42	
8	I		56	171	27	12.3	14.3	108	47	
9	I	+	56	168	22	11.2	13.2	92	47	Gas
10	I		57	160	19	12.3	12.8	109	47	Gas
11	I		57	168	24	12.6	15.0	110	47	
12	N		57	172	26	11.5	14.3	110	51	
13	?		57	165	23	11.2	13.7	100	56	Appendicitis
14	?		58	163	24	12.8	13.7	112	37	Wounded
15	I		58	168	25	11.4	13.2	94	52	
16	I		58	170	25	11.2	13.0	94	49	Gas
17	I		59	175	19	12.5	12.9	122	46	Gas
18	I ?		59	169	21	11.5	12.5	99	49	Bronchitis
19	?		59	166	25	11.5	14.0	108	48	
20	I	+	59	167	23	12.5	14.7	108	43	
21	E		60	172	25	12.7	13.6	100	34	Gas, rheumatism (?), dysentery
22	I		60	174	29	11.3	13.0	98	41	
23	E		60	171	25	12.4	14.2	110	42	
24	I		60	162	23	13.3	14.3	106	36	
25	I		60	164	29	13.3	15.1	109	45	Wounded
26	I		60	183	25	12.5	14.3	101	45	
27	I		60	174	21	10.8	13.0	96	46	
28	?		60	173	23	12.5	13.4	107	45	
29	I		60	170	24	12.5	13.7	104	43	
30	I	+	61	161	27	12.8	13.7	103	39	Wounded
31	I		61	174	24	11.8	12.7	102	35	Wounded, gas
32	I	+	61	168	29	10.5	12.5	92	44	Gas, shell shock
33	E		61	164	25	13.0	13.6	113	41	
34	I	+	61	176	27	11.7	13.8	95	47	Appendicitis
35	I		62	163	24	11.2	13.7	121	48	
36	I		62	166	30	14.2	14.6	124	39	
37	I		62	173	29	11.9	13.9	108	50	Gas
38	I	+	62	171	26	12.3	13.2	98	43	
39	?	+	62	173	25	12.5	14.6	109	44	Gas
40	E		62	170	29	13.0	15.0	105	42	Gas
41	E		63	172	50	12.8	11.8	84	32	Gas
42	I	+	63	163	33	14.0	15.0	109	33	
43	I		63	163	26	13.5	14.2	103	34	Gas, wounded, rheumatism (?)
44	I		63	174	40	13.8	14.0	112	42	Gas
45	?		63	169	21	13.5	14.9	130	44	
46	I		63	167	24	11.8	13.4	101	45	
47	I		63	164	21	12.8	14.0	127	45	Shell shock
48	I		63	169	28	12.0	14.0	109	51	
49	I		63	178	23	12.7	13.5	109	50	
50	I		63	170	23	11.3	13.5	97	48	
51	I	+	63	172	20	10.5	13.1	91	53	

Column 2 gives the phase of respiration in which the exposure is made.

Column 3 indicates (+) whether exposures were obtained both in inspiration and expiration.

Columns 4, 5 and 6 give the weights, height, and age.

Columns 7, 8, 9 and 10 give the transverse diameter, the long diameter, the area of the cardiac shadow and the cardiac angle.

Column 11 gives notes of interest.

TABLE 1.—Data and Measurements of the Hearts of the Soldiers Examined—(*Continued*)

No.	Phase Respiration	P.	Weight, Kg.	Height, Cm.	Age, Yrs.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Notes
52	I		64	167	20	14.4	14.6	125	36	
53	N		64	164	29	12.0	12.5	83	34	
54	E		64	174	23	12.8	13.5	102	38	Gas
55	E		64	167	31	12.7	13.8	104	38	Wounded
56	N		64	173	24	13.4	14.4	129	47	Gas
57	I	+	64	176	21	12.2	13.5	82	38	
58	I	+	64	167	24	12.5	13.9	100	38	Gas
59	I		64	181	29	11.2	13.5	96	45	
60	I		64	171	26	12.8	14.4	108	43	Trench fever ?
61	I	+	64	168	28	13.2	15.2	131	47	Gas
62	I		65	177	28	14.2	14.8	126	38	
63	I	+	65	175	28	13.3	14.6	119	40	
64	I		65	168	20	12.8	13.4	109	42	Gas
65	E		65	170	20	11.8	14.0	114	47	
66	I		65	176	21	12.8	13.3	112	45	Gas, shell shock
67	I	+	65	164	27	12.3	12.8	96	36	Wounded
68	I		65	172	27	12.8	14.0	111	44	
69	I		65	170	23	12.7	15.3	126	50	
70	E		65	170	20	11.2	13.2	95	48	
71	I	+	66	165	22	11.6	13.4	92	39	
72	I		66	164	27	13.5	15.4	126	40	Gas
73	E		66	182	25	12.2	13.6	101	44	
74	I		66	167	26	12.4	14.6	121	53	
75	I	+	66	179	19	12.3	14.5	108	49	
76	E		66	165	21	12.6	15.1	119	48	
77	I		67	161	25	14.5	14.8	109	30	Gas
78	I		67	173	29	14.6	15.3	124	38	Gas
79	I		67	167	25	13.7	15.2	120	38	
80	I	+	67	176	27	13.7	13.5	92	29	Gas
81	I		67	175	23	12.4	13.9	104	37	Gas
82	I		67	167	26	14.4	15.1	109	35	
83	I		67	175	28	12.4	13.0	96	35	
84	I		67	168	27	14.0	14.6	124	41	
85	I		67	169	23	13.2	13.1	94	32	Gas
86	I		67	170	24	15.0	16.3	157	41	
87	I		68	167	49	13.5	14.0	110	31	
88	E		68	171	24	15.0	15.5	129	39	
89	I		68	171	21	13.4	14.0	111	32	Gas
90	I		68	175	24	12.8	14.1	131	43	
91	I		68	174	18	11.8	12.8	99	36	Gas
92	?		68	170	26	13.8	15.1	118	41	
93	I	+	68	174	29	12.8	14.0	114	47	Gas
94	I		68	175	26	14.0	15.1	118	43	
95	?		68	176	23	12.1	15.4	140	55	Gas
96	I	+	68	178	23	13.0	15.5	140	49	Not in France
97	I		69	175	42	15.7	16.1	132	35	
98	N	+	69	180	26	12.7	13.8	108	35	
99	I	+	69	167	22	12.9	13.5	96	38	Gas
100	I		69	169	26	14.8	15.9	129	37	
101	I		69	174	31	13.8	15.1	122	40	Gas
102	E		69	177	23	12.6	14.1	120	41	
103	I		69	177	25	11.8	13.3	110	48	Gas
104	I	+	69	182	28	12.8	15.0	122	45	Gas, wounded
105	I	+	69	171	30	14.8	15.0	135	41	Gas, wounded
106	I		69	172	26	13.6	15.1	110	42	Gas
107	I	+	69	177	28	12.2	14.3	104	42	
108	I		69	180	28	12.3	13.2	106	49	
109	?		70	174	31	13.5	14.6	112	37	Gas
110	I	+	70	180	30	12.0	12.6	100	40	
111	I		70	171	30	12.8	13.2	96	35	
112	?		70	176	40	15.0	15.0	121	42	
113	I		70	176	29	13.3	14.3	109	36	
114	?		70	170	25	13.9	14.3	120	44	
115	I	+	70	175	24	13.0	14.6	114	40	
116	I ?	+	70	184	27	12.8	14.1	109	46	
117	I		70	175	22	11.8	15.0	109	51	
118	I		70	175	18	13.0	14.0	98	42	

TABLE 1.—Data and Measurements of the Hearts of the Soldiers Examined—(*Continued*)

No.	Phase Respiration	P.	Weight, Kg.	Height, Cm.	Age, Yrs.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Notes
119	I		71	172	22	13.7	15.8	122	35	
120	E		71	167	26	15.0	16.3	136	35	
121	?		71	169	36	14.0	13.8	121	37	
122	I		71	170	29	14.2	14.4	105	32	Gas
123	I		71	177	34	13.3	15.3	110	42	Dysentery ?
124	I	+	71	172	27	14.0	15.7	122	40	Measles
125	I		71	178	23	12.1	14.0	91	45	
126	I		71	172	23	11.3	13.3	91	43	
127	I		72	179	24	12.7	12.4	94	30	
128	I	+	72	167	24	14.2	14.6	110	37	
129	I		72	174	22	14.0	14.8	134	43	Wounded, buried
130	N		72	165	23	12.4	13.6	104	39	
131	I	+	72	178	24	13.0	15.2	124	45	
132	I		72	174	20	12.4	15.1	122	48	
133	I		72	174	29	14.7	15.7	127	42	
134	?		72	177	26	13.4	14.5	123	45	
135	I		72	173	21	12.8	15.3	127	52	
136	I	+	73	173	25	14.5	14.9	110	34	
137	I		73	178	21	14.1	14.8	119	38	
138	I		74	174	28	14.4	15.0	114	35	Gas
139	I	+	74	166	22	14.6	14.1	113	33	
140	I		74	171	24	13.7	14.7	110	34	
141	I		74	172	23	12.3	12.7	80	33	
142	I		74	172	25	13.0	14.3	115	45	
143	I		74	178	27	13.3	16.1	146	46	
144	I		74	186	23	12.7	14.3	96	41	
145	I	+	75	175	25	14.7	15.8	115	33	
146	I	+	75	170	28	13.2	14.4	95	37	
147	I		75	173	25	16.0	16.2	108	21	
148	I	+	75	172	25	12.0	13.2	100	39	
149	I		75	165	27	13.0	14.2	118	45	
150	I		75	175	30	13.2	15.3	114	41	
151	?		75	174	21	12.7	14.4	102	45	
152	N		75	175	24	11.0	14.1	111	56	
153	I	+	76	176	25	14.5	15.2	121	33	Febricula
154	I		77	179	28	12.2	15.0	127	48	
155	I		77	181	30	12.8	15.9	126	49	Trench fever ?
156	E		78	173	24	14.2	14.3	110	28	Gas
157	I		78	170	28	14.3	14.8	107	35	
158	I		83	180	27	14.3	15.8	120	29	
159	I	+	83	182	21	12.5	14.7	124	44	Wounded
160	I		83	179	26	13.8	16.6	127	46	
161	I		86	180	26	13.8	14.7	110	36	

persons expiration is not an active process, but is the release from inspiration. In these cases, the expiratory phase is represented by the neutral position (N, Table 1). A question mark in the table indicates that the ring was not identified in the plate; it swung beyond the plate. There is, however, a defect in this method. It is impossible to record on the plate the exact level of the respiratory phase at which the exposure was made. The method is subjective to the extent that to secure the photograph at the height of the respiratory phases, reliance is placed on the operator.

The measurements taken were those recommended by Moritz [7] and his followers. In the plates the right and left borders were traced, and the outline of the heart's shadow completed by joining arbitrarily the lines representing these. The long and transverse diameters were measured. The angle of inclination of the heart, that is to say, the angle formed by the long diameter and a line drawn to the cardiac apex at right angles with the median line, was recorded. The area of the cardiac outline was measured by the planimeter.

TABLE 2.—AVERAGES OF TABLE 1

No. of Cases	Weight, Kg.	Height, Cm.	Age, Yrs.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees
2	53	154	25	13.0	13.5	98	37
2	54	163	30	11.9	13.2	97	43
1	55	158	29	12.8	14.5	122	42
4	56	167	24	12.8	14.2	106	44
4	57	166	23	11.9	14.2	107	50
3	58	167	24	11.8	13.3	100	46
4	59	169	22	12.0	13.7	111	46
9	60	171	24	12.3	13.8	103	41
5	61	168	26	11.9	13.2	101	41
6	62	169	27	12.5	14.1	110	44
11	63	169	28	12.6	13.8	105	43
10	64	170	26	12.7	13.9	106	40
9	65	171	23	12.6	13.9	112	43
6	66	170	23	12.4	14.4	111	45
10	67	170	25	13.7	14.4	110	35
10	68	173	25	13.2	14.5	122	41
12	69	175	28	13.3	14.5	117	41
10	70	175	27	13.1	14.2	108	41
8	71	172	27	13.4	14.8	112	28
9	72	173	23	13.2	14.5	118	43
2	73	175	23	14.3	14.8	114	36
7	74	174	24	13.4	14.4	110	38
8	75	172	25	13.2	14.7	107	39
1	76	176	25	14.5	15.3	121	33
2	77	180	29	12.5	15.4	126	48
2	78	171	26	14.2	14.5	108	31
3	83	180	24	13.5	15.7	123	43
1	86	180	26	13.8	14.7	110	36

In measuring fifty-six pairs of roentgenograms (Tables 3 and 4) it was found that in inspiration and in expiration the transverse diameter was identical in six pairs, greater in inspiration in thirty-one pairs and smaller in nineteen pairs. The long diameters were identical in three pairs, greater in inspiration in forty-two pairs, and smaller in eleven pairs. The area was greater in inspiration in forty-four pairs, smaller in twelve pairs. The angle of inclination was identical in three pairs, greater in inspiration in thirty-nine pairs, and smaller in four-

7. Moritz, F.: Ueber Veränderungen in der Form, grösse und Lage des Herzens beim Uebergang aus horizontalen in vertikale Körperstellung. Zugleich ein zweiter Beitrag zur Methodik der Orthodiagraphie, insbesonders zu der Frage wie die Orthodiagramme auszumessen seien und welche Körperstellung für die Orthodiagraphie des Herzens zu wählen sei, Deutsch. Arch. f. klin. Med. **82**:1, 1905.

teen pairs. But the difference in size and the difference in position was not great. The transverse diameters (less subject to error, as will be pointed out later, than the long diameter, because it does not require the arbitrary location of the apex) differed 5 mm. or less in forty-two

TABLE 3.—Measurements of the Cardiac Shadow in Inspiration and Expiration, and the Difference Between the Two

No.	Inspiration				Expiration				Difference Between Inspiration and Expiration			
	Area, Sq. Cm.	Long Diameter, Cm.	Transverse Diameter, Cm.	Angle, Degrees	Area, Sq. Cm.	Long Diameter, Cm.	Transverse Diameter, Cm.	Angle, Degrees	Area, Sq. Cm.	Long Diameter, Cm.	Transverse Diameter, Cm.	Angle, Degrees
1	106	14.1	13.3	32	116	14.4	13.3	35	−10	−0.3	0.0	− 3
2	101	15.0	13.7	33	99	14.5	14.4	29	+ 2	+0.5	−0.3	+ 4
3	88	12.2	12.7	33	78	11.9	12.5	31	+10	+0.3	+0.2	+ 2
4	92	13.5	13.7	29	83	12.7	12.8	29	+ 9	+0.8	+0.9	0
5	95	13.0	13.0	35	85	12.5	12.7	34	+10	+0.5	+0.3	+ 1
6	109	15.0	14.4	33	102	14.6	14.0	32	+ 7	+0.4	+0.4	+ 1
7	115	15.8	14.7	33	112	14.9	14.3	33	+ 3	+0.9	+0.4	0
8	121	15.3	14.5	32	103	13.4	14.0	27	+18	+1.9	+0.5	+ 6
9	113	14.1	14.6	33	117	14.7	14.7	33	− 4	−0.6	−0.1	0
10	100	13.6	12.0	40	97	13.1	12.5	39	+ 3	+0.5	−0.5	+ 1
11	110	14.6	14.2	37	95	13.4	12.7	38	+15	+1.2	+1.5	− 1
12	90	12.9	12.2	36	94	13.0	12.4	34	− 4	−0.1	−0.2	+ 2
13	114	13.9	12.8	34	96	12.8	11.6	39	+18	+1.1	+1.2	− 5
14	108	13.8	12.7	35	102	13.7	12.6	36	+ 6	+0.1	+0.1	− 1
15	109	14.7	12.5	40	104	13.9	13.2	36	+ 5	+0.8	−0.7	+ 4
16	95	14.4	13.2	37	98	14.4	13.6	34	− 3	0.0	−0.4	+ 3
17	110	14.9	14.5	34	107	14.9	14.3	35	+ 3	0.0	+0.2	− 1
18	112	14.5	14.0	41	104	13.9	13.4	35	+ 9	+0.6	+0.6	+ 6
19	103	13.7	12.8	39	100	13.9	13.0	38	+ 3	−0.2	−0.2	+ 1
20	92	13.4	11.6	39	96	12.8	11.2	40	− 4	+0.6	+0.3	− 1
21	95	13.3	12.0	43	93	13.0	11.7	39	+ 2	+0.3	+0.3	+ 4
22	96	13.5	12.9	38	98	13.4	13.2	35	− 2	+0.1	−0.3	+ 3
23	122	16.2	14.0	39	108	14.6	13.5	34	+14	+1.6	+0.5	+ 5
24	100	13.2	12.0	39	106	13.5	12.9	35	− 3	−0.3	−0.9	+ 4
25	109	14.5	13.8	41	104	13.7	13.5	34	+ 5	+0.8	+0.3	− 7
26	132	14.8	13.7	42	112	14.3	13.5	36	+20	+0.5	+0.2	+ 6
27	128	14.8	13.3	44	124	14.5	13.0	45	+ 4	+0.3	+0.3	− 6
28	82	13.5	12.2	38	85	13.0	12.2	39	− 3	+0.5	0.0	− 1
29	119	14.6	13.3	40	95	12.4	12.8	42	+24	+2.2	+0.5	− 2
30	122	15.7	13.4	41	108	14.1	13.4	38	+14	+1.6	0.0	+ 3
31	100	13.9	12.5	38	91	13.8	12.6	37	+ 9	+0.3	−0.1	+ 1
32	92	12.5	10.5	44	80	12.3	10.3	37	+12	+0.2	+0.2	+ 7
33	120	13.9	13.9	43	107	13.5	12.8	40	+13	+0.4	+1.1	+ 3
34	114	14 0	12.8	47	102	13.0	12.0	36	+12	+1.4	+0.8	+11
35	98	13.8	12.4	42	104	14.4	13.3	38	− 6	−0.6	−0.9	+ 4
36	122	15.7	14.0	40	110	15.8	13.9	39	+12	−0.1	+0.1	+ 1
37	114	14.6	13.0	40	105	14.0	13.0	42	+ 9	+0.6	0.0	− 2
38	132	15.0	12.8	45	115	14.5	12.7	41	+17	+0.5	+0.1	+ 4
39	95	13.8	11.7	47	90	13.1	11.7	41	+ 5	+0.7	0.0	+ 6
40	124	14.7	12.5	44	104	13.9	13.6	37	+20	+0.8	−1.1	+ 7
41	140	15.5	13.5	49	124	14.7	13.0	40	+16	+0.8	+0.5	+ 9
42	124	15.2	13.0	45	103	13.8	12.4	38	+21	+1.4	+0.6	+ 7
43	86	13.3	11.4	40	82	13.1	11.9	35	+ 4	+0.2	−0.5	+ 5
44	109	14.1	12.8	46	102	14.1	12.2	41	+ 7	0.0	+0.6	+ 5
45	108	14.5	12.3	49	96	13.6	12.8	38	+12	+0.9	−0.5	+11
46	109	13.8	12.8	42	108	14.0	13.0	41	+ 1	−0.2	−0.2	+ 1
47	93	13.2	12.3	43	80	12.6	12.2	37	+13	+0.6	+0.1	+ 6
48	92	13.2	12.2	47	100	13.5	11.5	50	− 8	−0.3	+0.7	− 3
49	104	14.3	12.2	42	94	14.0	12.3	35	+10	+0.3	−0.1	+ 7
50	109	14.6	12.5	44	98	13.1	12.2	41	+11	+1.5	+0.3	+ 3
51	108	14.7	12.5	43	110	14.9	13.2	41	− 2	−0.2	−0.7	+ 2
52	91	13.1	10.5	53	87	12.5	10.6	54	+ 4	+0.6	−0.1	− 1
53	131	15.2	13.2	47	121	14.4	12.8	48	+10	+0.8	+0.4	− 1
54	102	13.6	12.5	37	105	13.8	12.7	34	− 3	−0.2	−0.2	+ 3
55	135	15.0	14.8	41	117	14.1	14.3	33	+18	+0.9	+0.5	+ 8
56	96	12.8	12.3	36	87	12.7	12.3	32	+ 9	+0.1	0.0	+ 4

+ indicates that inspiration is greater than expiration.
− indicates that inspiration is smaller than expiration.

pairs, and 1.0 cm. or less in fifty-two pairs. The long diameters differed 5 mm. or less in thirty pairs, and 1.0 cm. or less in forty-eight pairs. The areas differed by 5.0 sq. cm. or less in twenty-two pairs, and by 10.0 sq. cm. in thirty-seven pairs. Significant differences in size, therefore, do not usually occur during the inspiration and expiration of normal breathing. But the fact that arrests attention is that the heart shadows are larger, that they have longer diameters and that during inspiration the angles increase. There appears no reason to doubt that in certain individuals decrease in these measurements

TABLE 4.—Differences in the Measurements Tabulated Between Inspiration and Expiration

Area					Long Diameter				Transverse Diameter				Angle	
Sq. Cm.	No. of Cases				Cm.	No. of Cases			Cm.	No. of Cases			Degrees	Cases
+24	1													
+22					+2.2	1								
+21	1				+2.1									
+20	2				+2.0									
+19					+1.9	1								
+18	3				+1.8									
+17	1				+1.7									
+16	1				+1.6	2								
+15	1				+1.5	1			+1.5	1				
+14	3				+1.4	1			+1.4					
+13	3				+1.3				+1.3					
+12	4				+1.2	1		42	+1.2	1				
+11	1			44	+1.1	1			+1.1	1			+11	2
+10	4				+1.0	1			+1.0				+10	
+ 9	5				+0.9	3			+0.9	1			+ 9	1
+ 8					+0.8	6			+0.8	1		31	+ 8	1
+ 7	2				+0.7	1			+0.7	1			+ 7	4
+ 6	1				+0.6	5			+0.6	3			+ 6	4
+ 5	3				+0.5	6			+0.5	5			+ 5	3
+ 4	3				+0.4	2			+0.4	3			+ 4	7
+ 3	4				+0.3	5			+0.3	6			+ 3	6
+ 2	2				+0.2	2			+0.2	4			+ 2	3
+ 1	1	22	37		+0.1	3	30	48	+0.1	4	42	52	+ 1	8
0					0	3		3	0	6		6	0	3
− 1					−0.1	2			−0.1	4			− 1	7
− 2	2				−0.2	4			−0.2	4			− 2	2
− 3	4				−0.3	3			−0.3	2			− 3	2
− 4	3				−0.4			11	−0.4	1			− 4	
− 5				12	−0.5				−0.5	3		19	− 5	1
− 6	1				−0.6	2			−0.6				− 6	1
− 7					−0.7				−0.7	2			− 7	1
− 8	1				−0.8				−0.8					
− 9									−0.9	2				
−10	1								−1.3	1				

+ indicates that inspiration is larger than expiration.
− indicates that inspiration is smaller than expiration.

takes place, but the study of the roentgenograms supplies no explanation for this occurrence. The reason may be sought, perhaps, in peculiarities in the motion of the thorax and of the diaphragm.

The comparison of roentgenograms made in normal inspiration and expiration then, permits the statement that the difference between the two is not great; that, as is expected, the size of the heart shadow is usually greater in inspiration; and that, in this phase, the angle of inclination is usually larger. For clinical purposes, therefore, as will be shown, in a method accompanied by variations so large, the influ-

ence of the phases of normal respiration on the size of the heart may be neglected.

The hearts were measured in 208 soldiers. Although the men who were sent were considered by themselves and by the officers who selected them sound and fit for service, forty-seven had, at one time or another, suffered from an acute infectious disease. The infections and the number of men affected were as shown in Table 5. Only the remaining 161 are considered, therefore, in this discussion (Table 1). For the sake of completeness and for the use of others making similar studies the data of the forty-seven other men are given (Tables 6 and 7).

TABLE 5.—Infectious Diseases Reported by the Rejected Soldiers

Disease	No. of Cases	Other Diseases	No. of Cases	Disease	No. of Cases	Other Diseases	No. of Cases
Typhoid fever	2			Dysentery...	2;	also Pneumonia.....	1
Trench fever..	2					Influenza.....	1
Influenza.....	11;	also Trench fever...	1			Trench fever and gas	1
Gas poisoning	6;	also Dysentery.....	2	Mumps.....	5;	also Gas poisoning.....	1
		Pneumonia.....	2	Pneumonia..	8		
		Rheumatism...	1	Scarlet fever	1		

Table 1 gives the following information: The phase of respiration in which each plate was secured; whether plates of both respiratory phases were taken; the weight, height and age; the transverse diameter, the long diameter, and area of the cardiac shadow, and the angle of inclination. Other measurements were not made; they were not considered of special value in this study.

In order to facilitate the study of the data, these are presented in the form of curves. Based on a study of his own [5] and on a collation of published figures, Bardeen [8] has constructed formulae from which he has drawn certain standard curves. In these he has shown that the transverse diameter and the area of the cardiac shadow vary with the weight of the body. For purposes of comparison, these so-called standards are utilized in the following discussion.

The transverse diameter of the heart is considered first. In Bardeen's curve this diameter at 53 kg. is 12.0 cm. (Fig. 1). From this point, the curve follows practically a straight line. The curve obtained in this study from the average measurements of soldiers, follows this with reasonable closeness. Between 56 and 66 kg. and at 74, 75, 77, 83 and 86 kg. the averages are below the standard. Elsewhere, they equal or exceed it. The differences are not sufficiently great to justify a conclusion that in respect to this dimension the hearts of the soldiers examined differ materially from the normal. The result of the examinations made by Smith [6] parallel these observations closely. Those

8. Bardeen, C. R.: Tables for Aid in the Determination of the Relative Size of the Heart by Means of the Roentgen Ray, Am. J. Roentgenol. 4:604, 1917.

TABLE 6.—Data and Measurements of the Hearts of the Soldiers Rejected

No.	Phase Respiration	P.	Weight, Kg.	Height, Cm.	Age, Yrs.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees	Notes
1	I		54	167	25	11.5	12.9	103	50	Typhoid fever
2	I	+	57	172	30	12.0	13.3	95	43	Influenza; trench fever
3	?		58	165	25	13.3	14.7	132	40	Influenza
4	I	+	58	164	25	13.3	14.8	128	44	Gas
5	I		58	161	20	12.4	13.0	96	48	Pneumonia
6	I		58	172	21	11.5	13.6	105	54	Gas
7	I		59	172	24	10.3	13.8	115	59	Influenza
8	I	+	60	167	26	12.4	13.8	98	42	Gas; dysentery
9	I	+	60	163	22	12.8	13.8	109	42	Rheumatism; gas
10	I		61	176	26	12.9	14.2	97	39	Dysentery
11	I		61	168	21	11.2	13.1	88	44	Mumps; gas
12	I		61	173	22	12.5	14.5	128	48	Gas; dysentery
13	I		62	165	25	13.7	15.4	134	40	Mumps
14	I		62	161	29	12.5	14.2	110	42	Gas
15	I	+	63	162	19	12.7	12.2	88	33	Typhoid
16	E		63	171	23	11.5	12.6	91	43	Mumps
17	I		63	174	26	12.0	13.8	118	52	Gas
18	I		63	174	23	11.0	12.7	94	44	Dysentery; pneumonia
19	I		63	175	24	12.9	15.4	131	55	Gas; pneumonia
20	I	+	64	162	22	13.8	14.5	109	41	Mumps
21	I	+	65	169	30	14.0	14.5	113	41	Mumps—kidneys ?
22	I	+	65	171	22	13.7	14.8	132	42	Dysentery; gas; trench fever
23	N	+	66	178	29	12.5	14.7	109	40	Influenza
24	I		66	176	25	12.4	15.7	131	57	Dysentery; influenza
25	I	+	67	168	34	13.3	14.1	106	32	Influenza
26	I		67	172	24	11.8	13.6	110	47	Pneumonia
27	I		67	173	23	12.8	15.1	124	47	Dysentery
28	E		67	172	23	13.0	13.9	104	40	Influenza
29	I		67	179	21	12.8	14.7	119	44	Influenza
30	N		68	167	31	13.9	14.4	102	35	Gas; pneumonia
31	I	+	69	165	32	13.0	13.0	96	35	Influenza
32	I	+	69	173	26	13.4	15.7	122	41	Trench fever
33	I		70	173	19	14.7	15.2	125	42	Gas
34	I		70	175	22	14.0	14.6	122	44	Trench fever
35	I		71	173	23	13.8	15.2	108	38	Influenza
36	I		72	178	26	15.5	16.4	196	57	Influenza
37	I		72	169	23	11.8	13.6	115	51	Gas
38	I	+	73	173	23	13.7	15.0	101	33	Scaret fever
39	I		74	176	22	13.8	14.8	133	34	Influenza
40	I		74	163	31	13.5	14.6	113	33	Influenza
41	I	+	74	176	26	14.0	16.2	122	30	Pneumonia
42	I		75	172	29	14.2	14.3	113	36	Pneumonia
43	I		75	168	28	14.4	15.8	125	52	Pneumonia
44	I ?	+	76	176	26	12.2	12.9	90	36	Pneumonia
45	I		80	183	23	14.3	14.5	103	25	Pneumonia
46	I		82	171	32	13.7	14.5	120	42	Pneumonia
47	N	+	86	176	25	12.8	13.9	114	34	Mumps

Column 2 gives the phase of respiration in which the exposure is made.

Column 3 indicates (+) whether exposures were obtained both in inspiration and expiration.

Columns 4, 5, 6 give the weight, height, and age.

Columns 7, 8, 9 and 10 give the transverse diameter, the long diameter, the area of the cardiac shadow, and the cardiac angle.

Column 11 gives notes of interest.

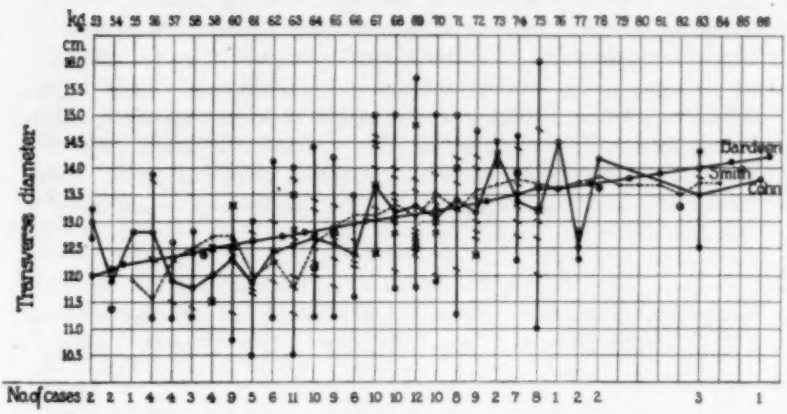

Fig. 1.—The Transverse Diameter.—The ordinates give the diameter; the abscissae the body weight. Below the curves is stated at each weight the number of cases examined at that weight, on which the average is based. The vertical lines represent the range of observations at that weight; the short oblique or horizontal lines which cross these indicate the measurement of each case examined. For comparison the standard curve of Bardeen is given. Smith's curve is likewise shown. × indicates Meakin's and Gunson's average measurement of the hearts of "irritable soldiers."

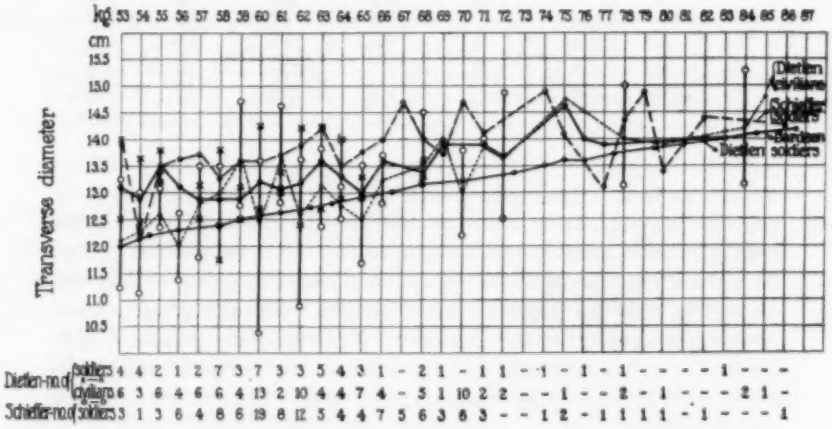

Fig. 2.—The Transverse Diameter.—The ordinates give the diameter; the abscissae the body weight. The dotted line represents Dietlen's civilians. The heavy broken line represents Schieffer's soldiers. For comparison the light unbroken line representing the standard curve of Bardeen is given; and the heavy line represents Dietlen's civilians. The vertical lines at each weight represent the range of Dietlen's observations; x————x, the range for soldiers; o————o, the range for civilians. Below the curve at each weight is stated the number of observations at that weight, on which the average is based.

made by Meakins and Gunson [9] are, on the whole, smaller than the foregoing, but their measurements were taken of the hearts of soldiers who suffered from the "Irritable Heart." Dietlen's [10] figures (Fig. 2), on the other hand, both for soldiers and civilians, are a little larger, those for soldiers falling at every weight above the standard, those for civilians falling below it five times. Schieffer's[11] curve (Fig. 2), based on the examination of soldiers in Moritz's clinic, is, on the whole, farther still above the standard; once it coincides with it, and twice it falls below it.

TABLE 7.—AVERAGES OF TABLE 6

No. of Cases	Weight, Kg.	Height, Cm.	Age, Yrs.	Transverse Diameter, Cm.	Long Diameter, Cm.	Area, Sq. Cm.	Angle, Degrees
1	54	167	25	11.5	12.9	103	50
1	57	172	20	12.0	13.2	95	43
4	58	165	22	12.6	14.0	115	45
1	59	172	24	10.3	13.8	115	59
2	60	165	24	12.6	13.8	108	42
3	61	172	23	12.1	13.9	104	40
2	62	163	27	13.1	14.8	124	41
5	63	171	23	12.0	13.3	104	45
1	64	162	22	13.8	14.5	100	41
2	65	170	26	13.8	14.8	122	41
2	66	177	27	12.4	15.2	120	48
5	67	172	27	12.7	14.2	112	42
1	68	167	21	13.0	14.4	102	35
2	69	169	29	13.2	14.3	108	38
2	70	174	20	14.3	14.9	123	43
1	71	173	23	13.8	15.2	103	38
2	72	173	24	13.6	15.0	125	44
1	73	173	23	13.7	15.0	101	33
3	74	171	26	13.7	15.2	122	35
2	75	167	28	14.3	15.0	119	44
1	76	176	26	12.2	12.9	90	36
1	80	183	23	14.3	14.5	103	35
1	82	171	22	13.7	14.5	120	42
1	86	176	25	12.8	13.9	114	34

Inasmuch as only the transverse diameter may be measured in an objective manner, being alone uninfluenced by the shadows of other viscera, especial importance is attached to this measurement. That divergencies appear in the several curves presented is not of so much interest as that the similarity is significant. Although in each series of examinations (Dietlen, Schieffer, Meakins and Gunson, Smith, Cohn) the number at each weight examined was not great, the curves show that at succeeding weights a gradual, even if not uniform,

9. Meakins, J. C., and Gunson, E. B.: Orthodiagraphic Observations on the Size of the Heart in Cases of So-Called "Irritable Heart," Heart **7**:1, 1918.

10. Dietlen, H.: Ueber Grösse und Lage des normalen Herzens und ihre Abhängigkeit von physiologischen Bedingungen, Deutsch. Arch. f. klin. Med. **88**:55, 1906.

11. Schieffer: Ueber den Einfluss des Militärdienstes auf die Herzgrösse, Deutsch. Arch. f. klin. Med. **92**:392, 1908.

increase in length of this diameter occurs. Since these curves are based on averages, the range of the individual measurements which form the bases of them requires consideration. Bardeen's standard curve, it will be remembered, is constructed from a formula. The widest ranges observed in the present study were 3.5 cm. at 63 kg. (11 cases); 3.8 cm. at 69 kg. (12 cases) and 5.0 cm. at 75 kg. (8 cases). But at 63 kg., 8 of 11 cases fell within 2.0 cm.; at 69 kg., 7 of 12 cases fell within 1.2 cm.; at 75 kg., 5 of 8 cases fell within 1.2 cm. The ranges which are usual are, therefore, not wide. In Dietlen's fifty-nine soldiers these were, for example: at 53 kg., 1.5 cm.; at 54 kg., 1.2 cm.; at 58 kg., 2.1 cm.; at 60 kg., 1.6 cm.; at 62 kg., 1.8 cm.; at 63 kg., 1.5 cm.; at 65 kg., 0.4 cm. If the civilians are included they were: at 53 kg., 2.8 cm.; at 54 kg., 2.5 cm.; at 58 kg., 2.1 cm.; at 60 kg., 3.9 cm.; at 62 kg., 3.3 cm.; at 63 kg., 1.8 cm.; at 65 kg., 1.8 cm.

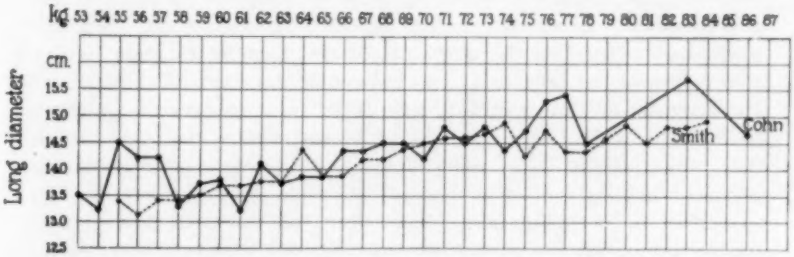

Fig. 3.—The Long Diameter.—The ordinates give the diameter; the abscissae the body weight. The unbroken line represents the curve of the present observations. Those of Smith are given for comparison. The number of men examined at each weight is the same as in Curve 1.

The curve of the average long diameter is compared with the curve obtained by Smith (Fig. 3). The two approximate each other closely. The difficulty of locating the apex precisely in the photographic plate makes the estimation of the long diameter inexact. The same difficulty is experienced in outlining and measuring the area of the heart's shadow. It is, therefore, considered under that head.

To delimit the area of the cardiac shadow requires that the extremities of the lines representing the right and left borders of the heart be joined by curved lines drawn arbitrarily. With experience these lines are probably drawn by different observers in a consistent manner, but no doubt each observer draws them differently. The outline, as Bardeen[5] points out, "will include within the territory of the heart the right and left atria and the cardiac extremity of the pulmonary artery and of the aorta. A small portion of the left auricle may be cut off by the line that curves toward the right from the left border, but as a rule this is insignificant." The outline is, therefore, as Bardeen says,

a modified outline of the heart. But the completed outline fails in exact representation also because of the difficulty, indeed, often because of the impossibility, of locating the apex in certain individuals. On being able to locate this point accurately depends the value of the measurement, both of the long diameter and of the area. Although the subject of heart disease is not considered in this paper, it may be pointed out that this difficulty is increased further in cases of heart failure, because the maneuver of exposing by deep breathing a length of the left border of the heart shadow sufficiently great to insure accuracy is often extremely difficult. Mention is made here of heart failure because a technic for the study of the size of the heart in this condition and in the stages which lead to it is a matter of concern in the clinic, where criteria for judging of size are earnestly wanted. For this reason, and in order to avoid the exaggeration in size due to deep breathing, the method of breathing while securing the roentgenograms was modified. In addition to the difficulty of locating the apex, the method of completing the outline from the apex to the right border also varies, as has been said, with individual observers. In this study, for instance, the lower outline was drawn in a conservative manner so that the cardiac area was less by several square centimeters than that which might have been obtained. Making exposures during normal breathing tended to increase this reduction, as the studies on the effect of deep breathing show. But, as has been pointed out, photographing in deep inspiration occasions an error in the other direction; it permits an increase in the volume of blood in the heart, and, consequently, in the area of its shadow, especially in the initial phase when the breath is held. Caution in respect to two other points should be expressed in considering the significance of this outline for clinical purposes. First, the line beginning at the junction of the right border with the diaphragm follows along the right border and passes beyond to the point where it joins the upper extremity of the left border, including within the outline most of the auricles and portions of the great vessels. This line does not follow or represent the ventricles. Second, the line joining the lower ends of the two borders, about the precise drawing of which, as has been said, there is the greater difficulty, is concerned with outlining the margin of one ventricle—the right ventricle. Of the entire cardiac shadow, therefore, only the line of the left border, and indeed, only a portion of this line, accurately follows a ventricular structure. It is, of course, appreciated that what has been said of the line of the right border applies to the value of the transverse diameter as well as to that of the area of the completed outline. No attempt is made at this time to estimate the precise importance of these points; they are matters which require consideration in the study of the abnormal heart.

Although the results depend on these variable factors, the curves (Fig. 4) based on the averaged observations of the area of the heart's shadow, show surprising similarities. The standard curve constructed according to Bardeen's formula is shown for comparison. The lowermost curve represents the averages of the observations obtained in this study. Except for the single observation at 55 kg., the curve lies below the standard. This position is expected in part, because the measurements were made from plates taken in the standing position. Curves based on the measurement of shadows obtained, as was the standard curve in the sitting position, have higher values. Bardeen estimates the reduction in size resulting from changing from the prone

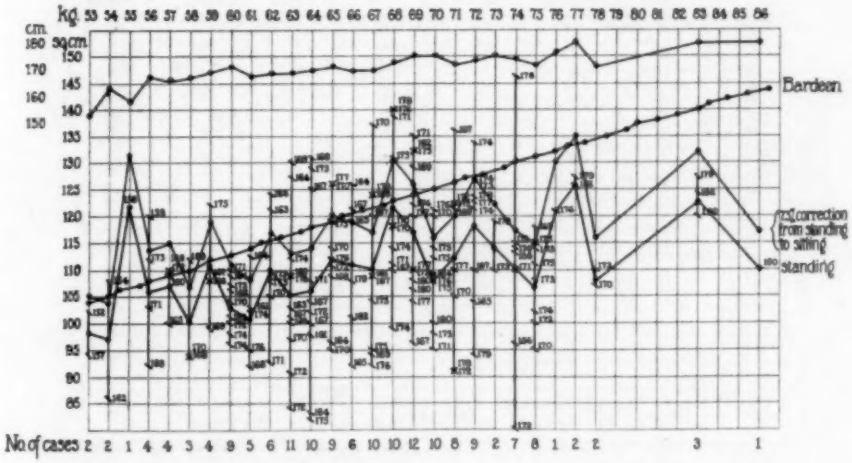

Fig. 4.—The Area of the Cardiac Shadow.—The ordinates give the area in sq. cm.; the abscissae the body weight. Below the curves is stated at each weight the number of men examined at that weight, on which the average is based. The vertical lines represent the range of observations at that weight; the short oblique lines which cross these indicate the measurement of each case examined. Opposite the short lines is placed the height of that individual. The lowest curve represents the average measurements actually observed in the standing position. The curve above and parallel with this is a corrected curve, giving the estimated area in the sitting position, 7.3 per cent. being added to the lower curve. For comparison the standard curve of Bardeen (the third curve from below upward) is given. The uppermost curve gives the average height of the men examined.

to the sitting position to be from 5 to 7 per cent., and the reduction from the prone to the standing position, 13.3 per cent. From the sitting to the standing position, a reduction, therefore, of 7.3 per cent. is expected. A correction of 7.3 per cent. was, therefore, made. The curve so corrected approximates the standard curve. The corrected

curve then exceeds the standard curve eleven times (53, 55, 56, 57, 59, 62, 65, 68, 69, 72, 77 kg.); it falls below it seventeen times (54, 58, 60, 61, 63, 64, 66, 67, 70, 71, 73, 74, 75, 76, 78, 83, 86 kg.).

It is important also to consider the range of observation at each weight from which the average curves are constructed, especially in applying data to the problem of the individual case. In the present study (Fig. 4 and Table 8) the greatest range is 64 sq. cm. at 74 kg. (seven cases); the smallest is 2.0 sq. cm. at 77 kg. (two cases). At

TABLE 8.—Body Weight According to Range of Cardiac Area

Range, Sq. Cm.	Weight in Kg.			Range, Sq. Cm.	Weight in Kg.		
	Cohn	Schieffer	Dietlen		Cohn	Schieffer	Dietlen
66	74	—	—	24	59	61	63
62	—	63	—	23	75	—	—
49	64	—	—	22	54	63	—
46	63	—	—	21	61	—	—
45	67, 71	—	—	20	—	55	64, 70
42	—	60	—	19	—	—	53, 55, 78
41	68	—	—	18	58	64, 71	56
40	72	—	—	17	—	75	66
39	69	—	—	16	—	—	54, 72
38	—	69	—	15	—	57	—
36	—	—	52	14	60	—	—
34	66	62, 56	—	11	—	59	59
33	—	65, 66	—	10	57	—	—
32	—	68	—	9	73	—	—
31	62, 65	—	—	8	53	—	—
29	—	—	60, 62	7	83	—	84
28	56	70	58	5	—	52	—
27	—	—	57, 61, 68	3	78	—	71
26	70	58	65	2	77	—	—
25	—	67	—				

TABLE 9.—Range of Cardiac Area of the Greater Number of Cases at Weights where the Greatest Ranges Occurred

Range, Sq. Cm.	Weight, Kg.	Range of Greater Number of Cases
66	74	4 of the 7 cases within 5 sq. cm.
49	64	5 of the 10 cases within 10 sq. cm.
45	71	5 of the 8 cases within 17 sq. cm.
45	67	6 of the 10 cases within 20 sq. cm.
46	63	7 of the 11 cases within 15 sq. cm.
41	68	5 of the 10 cases within 8 sq. cm.
40	72	6 of the 9 cases within 12 sq. cm.
40	60	7 of the 12 cases within 18 sq. cm.
34	66	Scattered through entire range
31	65	5 of the 9 cases within 10 sq. cm.
31	62	3 of the 6 cases within 4 sq. cm.
28	56	2 of the 4 cases within 9 sq. cm.

eight weights (53, 57, 58, 60, 73, 77, 78, 83 kg.) the range is less than 20 sq. cm.; it is between 21 and 30 sq. cm. in six instances (54, 56, 59, 61, 70, 75 kg.); between 31 and 40 sq. cm. in five instances (62, 65, 66, 69, 72 kg.); between 41 and 50 sq. cm. in five instances (63, 64, 67, 68, 71 kg.), and once it is 66 sq. cm. (74 kg.). But where the range is greatest, as at 74 kg., four of the seven cases actually lie within 5 sq. cm. (Table 9). At other weights, likewise where the range is wide, the occasional case, rather than the greater number, is responsible

for the wide limits. The range does not appear to be influenced by the weight (Table 10). For comparison the data of Dietlen and Schieffer are added.

A comparison of this result with the results obtained by others is instructive. The data published by Dietlen,[10] Schieffer,[11] Bardeen,[8] and Smith,[6] have, therefore, been arranged in curves in the same way. Dietlen's data include measurements of both soldiers and of male civilians. Separate curves for these two classes have been made. Arranged in this manner (Fig. 5), Bardeen's curve being included for comparison, the curve for soldiers coincides with the standard twice (54, 67); it lies above it thirteen times (52, 53, 56, 58, 59, 61, 63, 66,

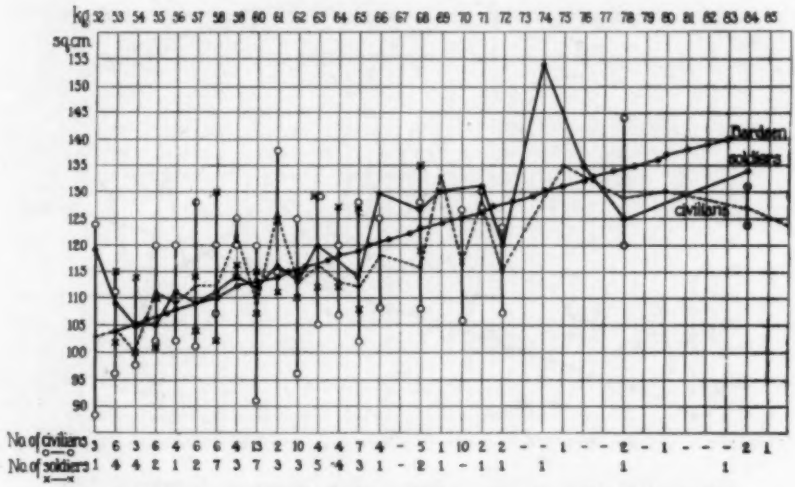

Fig. 5.—The Area of the Cardiac Shadow Based on Dietlen's Tables.—Ordinates and abscissae as in Curve 4. Below the curve is stated at each weight the number of soldiers and of civilian males examined at that weight, on which the average is based. The vertical lines represent the range of observations at each weight. o————o represents the range for civilians. x————x represents the range for soldiers. The standard curve of Bardeen is given for comparison.

68, 69, 71, 74, 76 kg.); and below it eight times (55, 60, 62, 65, 72, 78, 83 kg.). On the whole, therefore, it lies above rather than below. The curve for male civilians coincides with the standard twice (53, 63 kg.); it lies above it nine times (55, 56, 57, 58, 59, 61, 69, 71, 75 kg.); and below it thirteen times (54, 60, 62, 64, 65, 66, 68, 70, 72, 78, 80, 84, 85 kg.). This curve on the whole, then, lies below it. The soldiers' curve accordingly represents slightly larger hearts than that for civilians. And it exceeds the curve resulting from the present

study. With three exceptions Schieffer's curve (Fig. 6) lies uniformly above the standard and represents hearts larger than those in Dietlen's curve. Smith's curve (Fig. 7) follows the standard closely. It coincides with it seven times, falls below it twenty-two times and exceeds it once.

Interesting as is the comparison of the present curve with Bardeen's standard and the other curves, of greater importance is a consideration of the range. The ranges found by Dietlen extend from 3 to 36 sq. cm. (Fig. 5 and Table 8), and those found by Schieffer from 5 to 62 sq. cm. (Fig. 6 and Table 8). The widest range given by Smith is 11.0 sq. cm. (Fig. 7). It would be interesting to know the range of

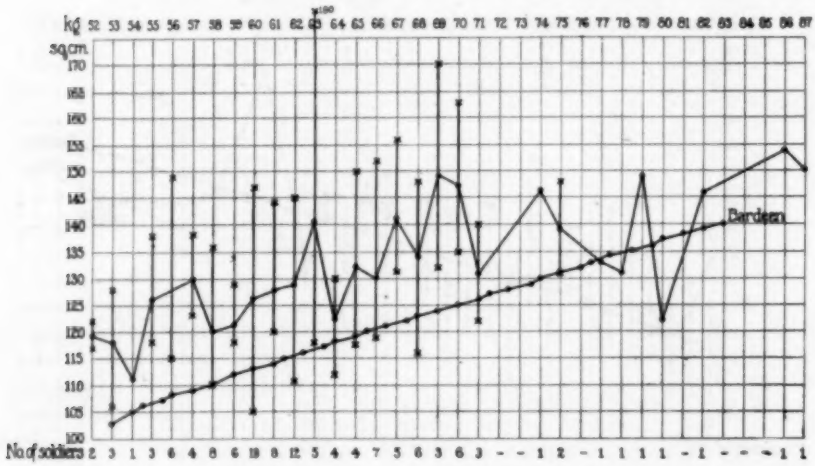

Fig. 6.—The Area of the Cardiac Shadow Based on Schieffer's Table.—Ordinates and abscissae as in Curve 4. Below the curve is stated at each weight the number of soldiers examined at that weight, on which the average is based. The vertical lines represent the range of observations at each weight. The standard curve of Bardeen is given for comparison.

observed areas at each weight in Bardeen's cases, but this information is not given in his papers. He gives, however, the average percentage of divergence from the standard curves for each 10 kg. of body weight for athletes. Between 51 and 60 kg. the deviation of the average area was 4.6 per cent. (B, Fig. 8) below the standard; between 61 and 70 kg. it was 4.4 per cent. above; between 71 and 80 kg. it was 2.7 per cent. above, and between 81 and 90 kg. it was 2.9 per cent. below. For comparison the deviations from the standard found in the study now presented are arranged in the same manner (C, Fig. 8). The percentage is based on the curve corrected for position of the body. For corre-

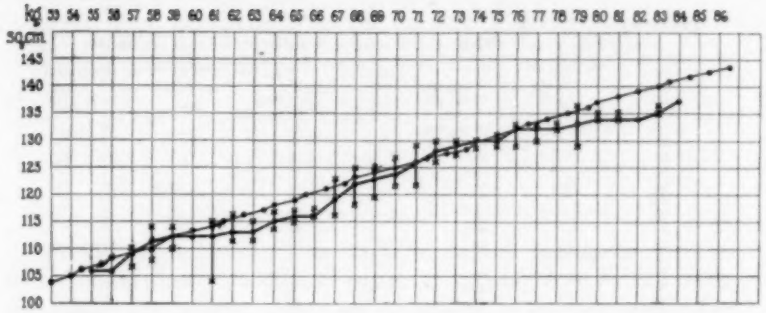

Fig. 7.—The Area of the Cardiac Shadow Based on Smith's Curve and Tables.—Ordinates and abscissae as in Curve 4. The vertical lines represent the range of measurements at each weight. The standard curve of Bardeen is given for comparison.

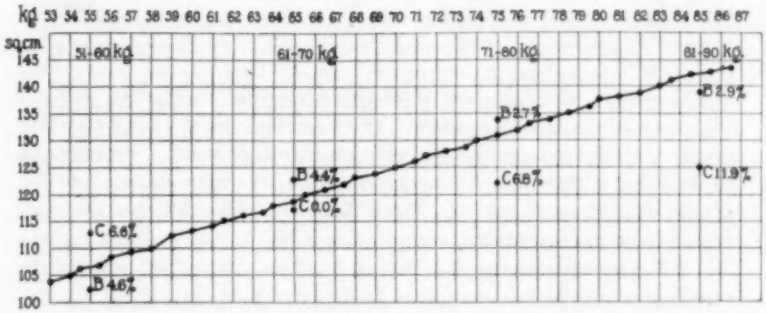

Fig. 8.—The standard curve of Bardeen is given. The average areas of the men examined at weights between 51 and 60, 61 and 70, 71 and 80, 81 and 90 have been inserted for the series now presented (C) and for the figures published by Bardeen (B). Opposite each is given the percentage deviation from the standard curve.

sponding weights they are 6.6 per cent. above, coincident with the standard, 6.8 per cent. below, and 13.8 per cent. below.

TABLE 10.—RANGE OF CARDIAC AREA ACCORDING TO BODY WEIGHT

Weight, Kg.	Range		
	Cohn	Schieffer	Dietlen
52	..	5 sq. cm.	26 sq. cm.
53	8 sq. cm.	22	19
54	22 sq. cm.	1 case	16
55	1 case	20 sq. cm.	19
56	28 sq. cm.	34	18
57	10	15	27
58	18	26	28
59	24	11	11
60	14	42	29
61	21	24	27
62	21	34	29
63	46	62	24
64	49	18	20
65	31	33	26
66	34	33	17
67	45	25	..
68	41	32	27
69	39	38	1 case
70	26	28	20 sq. cm.
71	45	18	3
72	40	..	16
73	9	..	..
74	66	1 case	1 case
75	23	17 sq. cm.	1 case
76	1 case	..	1 case
77	2 sq. cm.	1 case	..
78	3	1 case	19 sq. cm.
79	..	1 case	..
80	..	1 case	1 case
81	..	..	..
82	..	1 case	..
83	7	..	1 case
84	..	..	7 sq. cm.
85	..	..	1 case
86	1 case	1 case	..
87	..	1 case	..

The curves, then, all show a progressive, even if irregular, increase in the area of the heart's shadow. The usefulness of so-called standard curves, constructed from observed averages, depends, however, on the closeness with which the measurements of the individuals observed, approximate to these curves. Here there is a difficulty, for the wide range of the measurements reduces the value of the average figures. This difficulty apparently does not depend on the technic nor on the individual observer, for it appears in the curves of each.

It has been shown by Dietlen and others that the heart increases in size with the body height. This result is expected because of the usual relation of height to weight. In general therefore, the curves plotted for weight and for height should be similar. The heights of these 161 soldiers have been averaged and plotted at each kilogram of weight (Fig. 4). At 53 kg. the height is 153 cm. From here the curve ascends not quite in a regular fashion to 83 kg. where the height is 180 cm. The height of each individual examined has also been introduced in the curve (Fig. 4) on the vertical lines representing range,

opposite the point indicating the area of the cardiac shadow of each individual. The heights at each weight as the curve shows vary through an extended range (Table 11). Under these circumstances, the suggestion quoted by Schieffer that the area is numerically equal to the height less 50, is scarcely tenable.

TABLE 11.—RANGE OF HEIGHT AT VARIOUS BODY WEIGHTS

Height, Cm.	Weight, Kg.	Height, Cm.	Weight, Kg.	Height, Cm.	Weight, Kg.
21	69	14	70, 72	9	59
20	74	13	65	7	58
19	66	12	57	5	58, 73
17	64	11	63, 68, 71	3	78, 83
15	56, 61, 67, 69	10	62, 75	2	54, 77

Finally, the relation of the angle of cardiac inclination to other measurements has been studied, but there appears to be no rule relating this to the weight, height, or to any other measurement. The introduction of the use of the angle to express what is now indicated by the phrases "transversely lying heart" or "vertically hanging heart" or "pendulous heart" may, however, simplify reference to this phase of physical examination.

SUMMARY AND DISCUSSION

The attempt was made in this study to learn the size, in comparison with that of civilians, of the hearts of soldiers who had undergone the exertion of actual warfare. The data of soldiers available for comparison are those of Dietlen, Schieffer and Meakins and Gunson; and for civilians those of Dietlen. Dietlen's curve for area in general resembles Bardeen's standard; Schieffer's exceeds it; the one now presented is a little below it. The differences among the three are probably due to differences in technic of the observers. For transverse diameters, Dietlen's curve lies above Bardeen's standard, the present one lies below it. Schieffer's curve is higher than Dietlen's. If allowance were made (13 per cent.) for the differences between the lying and the standing position, the present curve would exceed Dietlen's and equal Schieffer's. The curves for area and transverse diameters given by Dietlen for civilians differ slightly, but not materially, from those of soldiers. The curves, therefore, do not indicate that soldiers exposed as were these, exhibit larger hearts than normal individuals. Against this conclusion must be set the post-mortem figures given by Karsner [12] for the hearts of British soldiers who were 27 years of age, and who had served twenty-two months. These were

12. Karsner, H. T.: Acute Endocarditis Following War Wounds, Including Notes of Heart Weight and Arteriosclerosis in Soldiers, Arch. Int. Med. **22**:296, 1918.

larger than the controls. If the requirements set by Karsner are sound, enlargement may not be expected in our soldiers whose average age was 24 and whose length of service was usually less than twenty-two months. Furthermore, the examinations here reported were conducted in May, 1919, six months after the cessation of hostilities. Although within that period many had undergone severe exertion, the amount of work they performed probably decreased. A diminution in size of the heart from the maximum reached in November, 1918, may have taken place, but no data are available to indicate whether decreasing the amount of work affects the subsequent size of the heart.

The technic differed from that usually employed in that the plates were taken for the most part during normal inspiration. There is a twofold reason for this; first, it avoids the increase of the heart's size which occurs during deep inspiration. A more nearly normal heart is photographed. Second, it is more likely to provide a standard against which the pathologic heart may be measured. For, as has been pointed out, in increasing heart failure, it becomes progressively more difficult to utilize the method which obliges the subject to breathe deeply and to hold the breath. The technic here employed does not require holding the breath and avoids the artificially large heart. There would probably be no objection to this alteration in technic were it not that exposures made in deep breathing lighten the lung fields, so permitting a sharper image of the heart, and expose in certain individuals, especially those in whom the angle of inclination of the heart is small, a greater extent of the heart's outlines. In the last point there is force. It is not, however, so cogent a reason as it appears to be, for deep breathing aids in locating the apex of the heart and in drawing the long diameter and the area. But these measurements are not superior in value to the transverse diameter, for this diameter increases with the body weight as do the others, it shows no greater variation at each weight, and it can be taken accurately without reference to respiration, and in any case involves no uncertainty such as is necessary in locating the apex and drawing the line indicating the border of the right ventricle.

The value for the present of so-called standard and average curves of cardiac measurements for use in the clinic is questioned. For this reason the range of the measurements for given weights has been emphasized. The difficulty in the use of these curves is illustrated in comparing the cardiac area of a soldier weighing 54 kg. with that of one weighing 86 kg. The areas of the two (Curve 4) are 108 sq. cm. and 110, respectively. And, again, in comparing the cardiac area of a soldier weighing 56 kg. with one weighing 83 kg., the areas of both being 120 sq. cm. Similar comparisons can be made in Dietlen's and Schieffer's curves (Figs. 5 and 6). For the clinic curves of this nature

do not solve the problem of supplying adequate criteria for judging the normality of a given heart. There is, still, necessity for more than a single criterion, such as size. In other connections these curves have a signal usefulness; they may, indeed, serve as bases for studies, in which, combined with other factors, satisfactory criteria for clinical use will be evolved.

CONCLUSIONS

1. In normal breathing the difference in the size of the heart during inspiration and expiration may be neglected.

2. The use of the transverse diameter of the heart shadow is a satisfactory measurement. It is as useful as and less uncertain than the long diameter or the area.

3. The range of the observed measurements interferes with the usefulness for the clinic of standard and average curves.

4. The hearts of soldiers examined under conditions stated are not larger than those of normal individuals.

TELEROENTGEN MEASUREMENTS OF THE HEARTS OF NORMAL SOLDIERS *

BERTNARD SMITH, M.D.
LOS ANGELES

Teleroentgen measurements were made on 277 men selected from the orthopedic service for the purpose of securing statistics on the heart size of soldiers who had had active fighting service overseas Only those men were selected for this study who had been free from cardiac symptoms during their period of military service and who had had no infectious disease since entering the army. Each man whose measurements are reported had completed his training without difficulty, had taken full part in forced marches overseas and had had at least three months of active fighting. Most of the measurements were taken immediately before the men were discharged from the hospital, and all the patients were well advanced in convalescence.

The same technic was followed throughout the series. All plates were from one to four seconds' duration, depending on the thickness from the plate. The upright of the tube stand was ruled in inches to correspond to the scale on the screen stand, and with plumbline markings for the lateral position of the tube, the adjustment to a position opposite the center of the plate could be made easily and quickly. When in position, facing the plate, the subject took a deep breath and then exhaled as completely as possible. After this he took a "half breath" on command and this was held for the exposure. Exposures were from one to four seconds' duration, depending on the thickness of the chest wall.

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* Report of studies made on the Cardiovascular Service, U. S. Army General Hospital No. 9, Lakewood, N. J.

NOTE.—The influence of work, such as military campaigning or training for athletic competition, on the size of the heart is still not satisfactorily known. It seemed unwise, therefore, to neglect the opportunity to study exactly the size of the hearts of soldiers after the campaign in France. To be most serviceable, the study should have been made in France in November, 1918. Unfortunately, proper facilities for doing the work were not available. Although less satisfactory, it was decided that information of sufficient usefulness could still be obtained after the return of troops to the United States. A number of soldiers were, therefore, examined simultaneously at U. S. General Hospital No. 9, at Lakewood, N. J., and at the Rockefeller Institute. The results of these studies are given in these papers by B. Smith and A. E. Cohn.

From the roentgenograms obtained in this way the following measurements were made:

1. Ml.: Distance from the midline to the most distant left border.
2. Mr.: Distance from the midline to the most distant right border.
3. T.D.: The sum of Ml. and Mr. has been taken for the value of the transverse diameter.
4. L.D.: The maximum long diameter, measured from the right auricular notch to the most distant apical border.
5. B.D.: The maximum broad diameter, measured at right angles from the long diameter to the most distant borders above and below.
6. The angle formed by the transverse and long diameters.
7. Diameter of the aortic arch.
8. The parallel ray silhoutte area,[1] estimated with the planimeter. From this area the volume was calculated by Bardeen's formula.[2]

In Table 1 the figures for transverse diameters, long diameter and areas are compared with the Dietlen [3] and Bardeen [4] tables for normals. Dietlen's figures were obtained by the orthodiagraphic method, with the subjects recumbent, and the Bardeen measurements were made with the subjects in the sitting position. Bardeen states that the transverse diameter is about 7 per cent. less for the standing than for the recumbent position. This possible variation with a difference of position has not been considered in the tables of this report, but the figures given are the measurements as made from the plates. The Bardeen figures in Table 1 are the approximate values for the ranges of weight.

TABLE 1.—Comparison of Diameters and Area with the Dietlen and Bardeen Normals

Weight, Kg.	Soldiers				Dietlen Table				Bardeen Table	
	Cases	T. D., Cm.	L. D., Cm.	Area, Cm.	Cases	T. D., Cm.	L. D., Cm.	Area, Sq. Cm.	T. D., Cm.	Area, Sq. Cm.
55–59	40	12.5	13.6	111	39	12.9	14.0	112	12.4	110
60–64	82	12.1	13.9	113	54	13.1	14.1	114	12.7	116
65–69	61	13.1	14.1	118	24	13.2	14.5	118	13.0	121
70–74	50	13.5	14.6	127	18	13.4	14.8	122	13.4	128
75–79	35	13.7	14.5	131	5	14.3	15.5	131	13.7	134
80–84	9	13.7	14.7	135	5	14.4	15.3	133	14.0	140

The figures for diameter and area from the soldiers are all well within the normal range. If the measurements are averaged for the ranges in body weight, and the comparison to the normal tables is expressed in percentages, the variation is very slight. In Table 2 the measurements from the 277 soldiers are given as percentages of the Dietlen and Bardeen figures. It should be remembered, that the soldiers had been in hospitals for several months, convalescing from leg and arm wounds, and during this period of inactivity many had

1 Bardeen, C. R.: Am. J. Roentgenol. **4**:604, 1917.
2. Bardeen, C. R.: Am. J. Anat. **23**:423, 1918.
3. Dietlen, H.: Deutsch. Arch. f. klin. Med. **88**:55, 1907.
4. U. S. Army X-Ray Manual, p. 414.

gained in weight to a figure above their normal. This gain was due more to an increase of fat than of skeletal muscle. In the table of individual measurements (Table 8) it is seen that the measurements show a greater variation from the normal (below normal) in those men with the higher weight.

TABLE 2.—PERCENTAGE RELATION OF MEASUREMENTS OF SOLDIERS WHEN COMPARED WITH THE DIETLEN AND BARDEEN NORMALS

Weight, Kg.	Dietlen Normals			Bardeen Normals	
	T. D., %	L. D., %	Area, %	T. D., %	Area, %
55-59	96	95	97	98	99
60-64	94	96	99	97	98
65-69	99	98	99	100	98
70-74	100	99	100	100	100
75-79	95	94	100	100	99
80-84	96	96	100	99	97

The heart measurements from the soldiers differ but very little from the normals when compared by weight. For the total series the transverse diameters average about 5 per cent. less than the Dietlen measurements, and 1 per cent. less than the normals of Bardeen. The long and broad diameters have a general average of 4 per cent. less than those of the Dietlen table. When the areas are compared it is found that the average with the soldiers' hearts is 1 per cent. less than Dietlen's normals and 15 per cent. below the figures given by Bardeen.

Dietlen [3] has compared his normal measurements by height, and in Table 3 the figures for this series are grouped for the same height ranges. The measurements for area and for the three diameters come within 3 per cent. of the Dietlen normal figures.

TABLE 3.—MEASUREMENTS COMPARED BY HEIGHT WITH DIETLEN'S NORMALS

Height	Soldiers						Dietlen's Normals					
	Cases	Ml., Cm.	Mr., Cm.	L. D., Cm.	B. D., Cm.	Area Sq. Cm.	Cases	Ml., Cm.	Mr., Cm.	L. D., Cm.	B. D., Cm.	Area Sq. Cm.
155-164	18	4.0	8.3	13.3	9.9	111	72	4.1	8.7	13.8	9.9	109
165-174	174	4.1	8.5	13.1	10.2	118	77	4.2	8.8	14.1	10.3	116
175-187	185	4.3	8.7	14.2	10.7	122	29	4.4	9.1	14.8	10.7	127

Measurements of the transverse diameter may have a wide range even with the same body weight. In the twenty-two cases with a body weight of 59 kilograms (Table 4), the transverse diameters range from 11.5 cm. to 14.0 cm. Also, a heart with a transverse diameter of 12.7 cm. may have a slightly larger area than the heart with a diameter of 14.0 cm. If other diameters are measured, this variation in the transverse figures is found to be due to the general heart shape. There is danger of serious error if an opinion of heart size is based on a measurement of the transverse diameter alone, especially in individual

cases, without attention having been given to the general form and position of the heart. The angle formed by the transverse and long diameter can often be of value in deciding the question of size in doubtful cases, especially when the area has not been determined.

TABLE 4.—MEASUREMENTS OF THE TRANSVERSE, LONG AND BROAD DIAMETERS, WITH AREA AND CARDIAC ANGLE, GROUPED BY WEIGHT

Weight, Kg.	Cases	Height Cm.	Age	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area Sq. Cm.	Aortic Arch, Cm.	Angle Degree
55	2	170	24	11.9	13.4	10.0	106	4.7	50
56	1	165	23	11.6	13.1	9.6	106	4.4	55
57	4	167	24	12.3	13.4	9.8	108	4.5	42
58	11	168	24	12.5	13.4	9.8	111	4.6	42
59	22	170	26	12.7	13.5	9.8	112	4.6	44
60	1	175	23	12.7	13.7	10.1	112	4.7	47
61	26	172	24	12.0	13.7	10.4	112	4.6	43
62	12	171	25	12.3	13.8	10.1	113	4.5	42
63	26	172	25	11.8	13.8	10.3	113	4.5	42
64	17	175	24	12.6	14.4	10.6	115	4.6	43
65	14	175	25	12.9	13.9	10.7	116	4.7	43
66	4	176	25	13.1	13.9	10.5	116	4.5	48
67	14	174	26	13.1	14.2	10.6	119	4.6	41
68	19	175	25	13.3	14.2	10.6	122	4.6	45
69	10	174	25	13.1	14.4	10.5	123	4.6	39
70	15	178	26	13.5	14.5	10.6	124	4.7	44
71	14	175	27	13.3	14.6	10.6	126	4.7	46
72	10	177	26	12.6	14.6	10.5	128	4.6	39
73	5	175	28	13.7	14.7	10.3	129	4.9	38
74	6	180	27	13.8	14.9	10.3	130	4.7	42
75	13	177	28	13.7	14.3	10.6	130	4.7	40
76	8	178	26	13.6	14.7	10.8	132	4.7	44
77	6	174	26	13.7	14.4	10.7	132	4.7	37
78	2	176	26	13.8	14.4	10.4	132	4.6	42
79	4	179	24	13.7	14.7	10.5	133	4.6	42
80	2	179	29	13.7	14.9	11.2	134	4.8	48
81	3	174	28	13.7	14.5	10.8	134	4.7	37
82	1	173	25	13.5	14.8	10.7	134	4.5	41
83	2	178	27	13.7	14.8	10.9	135	4.7	34
84	1	185	38	13.7	14.9	11.4	137	4.5	46

TABLE 5.—DIAMETERS, AREA AND ANGLE COMPARED BY HEIGHTS

Height, Kg.	Cases	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Angle, Degree
155	2	12.0	13.5	10.1	111	50
157	2	13.1	12.8	9.6	111	35
160	6	12.7	13.3	10.1	112	43
163	8	12.2	13.4	9.9	111	42
165	11	12.7	13.5	10.1	116	40
168	80	12.9	14.0	10.3	118	38
170	26	12.9	14.1	10.4	120	41
173	44	13.3	14.1	10.2	119	42
175	36	12.6	14.2	10.2	119	46
178	62	13.0	14.1	10.2	123	44
180	32	13.2	14.4	10.6	127	43
183	8	13.5	14.6	10.5	127	42
185	8	13.5	14.5	10.8	128	43

The broad, low lying heart, which gives a wide transverse diameter, will have a small angle, and the long heart, often found in the long, narrow chest, will have a wide angle. In the 277 cases, the range of this angle is from 23 to 63 degrees, showing the wide range that is present in the shape of the normal heart. The general average for the angle in this series is 43 degrees. An angle of 40 degrees or less is found in 41 per cent. of these men. The long, narrow heart, usually

TABLE 6.—Relation of Area to Diameters and Angle in Cases with a Weight of 59 Kg.

Area, Sq. Cm.	Height, Cm.	Age	T. D., Cm.	L. D., Cm.	B. D., Cm.	Angle, Degree
110	166	25	11.5	13.5	9.5	48
111	157	23	12.3	13.2	9.6	44
111	160	24	12.4	13.3	9.8	46
111	163	22	12.1	13.8	9.7	41
112	165	29	12.6	13.6	9.6	40
112	168	24	12.6	13.7	9.4	41
112	175	30	12.8	12.5	9.7	54
112	178	22	12.3	12.5	9.8	48
112	178	27	12.5	13.7	9.9	47
113	168	26	12.8	13.8	9.7	40
113	170	30	12.8	13.5	9.8	47
113	173	24	12.7	13.6	9.8	49
113	173	27	12.9	13.4	9.8	41
113	173	28	12.7	13.9	9.9	40
113	175	19	12.9	12.6	10.1	42
113	175	21	12.8	13.6	9.8	49
113	175	27	12.7	12.9	10.3	44
113	178	30	14.0	13.7	9.1	29
114	165	23	13.5	13.9	9.7	32
114	170	23	13.6	13.0	9.9	40
114	170	22	12.7	14.1	9.7	54
114	173	28	12.7	13.9	10.3	38

TABLE 7.—Relation of Angle to Diameters and Area

Angle, Degrees	Cases	T. D.		L. D.		B. D.		Area	
		Range, Cm.	Average, Cm.	Range, Cm.	Average, Cm.	Range, Cm.	Average, Cm.	Range, Sq. Cm.	Aver., Sq. Cm.
23	1	.....	14.2	.....	14.3	.....	10.3	.....	130
24	2	13.4-14.3	13.9	14.2-14.5	14.4	10.3-10.4	10.3	126-133	130
26	3	13.6-14.3	13.9	12.0-14.1	13.3	9.4-10.4	10.1	112-134	122
27	2	12.7-13.9	13.8	14.0-14.3	14.2	10.0-10.7	10.4	126-131	129
28	2	13.8-14.0	13.9	13.8-14.3	14.1	10.1-10.2	10.1	127-132	129
29	3	13.5-14.0	13.8	12.7-14.1	13.6	9.1-10.2	9.8	113-129	122
30	3	12.1-13.5	13.0	13.5-14.6	14.0	10.3-10.7	10.4	113-125	119
31	4	12.2-13.5	12.8	13.7-14.3	14.0	10.4-10.6	10.5	112-116	114
32	7	13.1-13.8	13.5	13.0-14.9	14.1	9.6-11.2	10.3	113-135	121
33	7	12.3-13.9	13.5	13.8-14.8	14.2	9.7-11.1	10.5	114-130	125
34	17	11.6-14.2	13.0	12.9-14.9	14.1	9.9-11.3	10.5	110-136	121
35	9	12.4-13.8	13.0	13.5-14.7	14.2	10.1-10.9	10.6	113-130	121
36	10	12.7-13.8	13.2	13.0-15.1	14.2	9.6-10.9	10.3	110-136	123
37	11	11.9-13.7	13.0	13.5-14.9	14.1	9.5-10.8	10.2	110-132	119
38	11	11.6-13.6	12.9	13.0-14.7	13.9	9.5-10.8	10.3	108-132	119
39	6	12.6-13.7	13.3	12.9-14.6	14.2	10.4-10.8	10.6	111-135	121
40	19	11.3-13.8	12.4	13.2-15.2	14.0	9.5-11.1	10.2	106-128	116
41	13	11.3-13.7	12.9	13.2-15.1	14.1	9.4-10.8	10.2	111-134	120
42	12	11.4-13.8	13.1	12.6-14.9	14.2	9.9-10.8	10.5	113-130	123
43	9	11.4-13.7	12.8	13.6-15.2	14.2	10.3-11.2	10.7	112-132	120
44	12	11.0-13.8	13.0	12.9-15.1	14.1	9.6-11.2	10.3	107-133	120
45	12	11.4-13.6	12.9	12.8-15.3	14.1	9.7-11.3	10.4	108-130	118
46	8	12.4-13.7	13.2	13.3-14.9	14.3	9.8-11.4	10.7	111-137	122
47	15	10.1-13.7	13.0	12.4-15.0	14.1	9.8-11.1	10.4	108-132	121
48	14	11.1-13.5	12.4	13.3-14.9	14.0	9.5-10.8	10.3	109-134	117
49	9	11.5-13.5	12.9	13.6-15.0	14.3	9.8-11.3	10.5	113-131	120
50	11	11.1-13.9	12.6	13.6-15.2	14.4	10.1-11.1	10.6	112-135	121
51	4	11.8-13.6	12.5	13.3-14.2	13.9	10.2-10.8	10.6	108-123	114
52	8	11.9-13.8	13.3	13.9-15.1	14.5	10.1-11.2	10.7	118-130	125
53	6	11.3-13.3	12.3	13.4-14.8	14.1	9.6-11.0	10.4	112-126	116
54	10	11.1-13.9	12.6	13.6-15.2	14.4	10.1-11.1	10.6	112-135	121
55	5	11.1-13.3	12.0	13.1-14.5	13.9	9.6-10.7	10.1	106-117	113
56	5	10.6-13.5	12.1	14.0-15.0	14.5	10.2-10.8	10.5	111-133	119
57	3	13.2-13.4	13.3	14.1-15.0	14.5	10.2-11.6	10.8	123-132	128
58	2	12.1-12.8	12.5	13.9-14.3	14.1	10.5-10.7	10.6	113-114	113
60	1	.....	11.6	.....	13.5	.....	9.8	.....	106
63	1	.....	11.6	.....	14.5	.....	11.0	.....	122

TABLE 8.—TELEROENTGEN MEASUREMENTS OF 277 NORMAL HEARTS OF SOLDIERS

No.	Wt., Kg.	Height, Cm.	Age	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Volume, C.c.	Arch, Cm.	Angle, Degrees
1	55	168	27	12.1	13.4	10.3	106	578	4.8	40
2	55	173	21	11.6	13.5	9.8	106	578	4.6	60
3	56	165	23	11.6	13.1	9.6	106	578	4.4	55
4	57	163	24	12.7	13.2	9.8	110	612	4.2	40
5	57	165	21	11.7	13.6	9.6	107	586	4.7	44
6	57	168	20	12.4	13.5	10.1	108	595	4.5	44
7	57	175	20	12.5	13.5	9.6	108	595	4.5	38
8	58	155	20	12.6	13.6	9.8	110	612	4.7	47
9	58	160	28	12.7	13.5	9.5	110	612	4.9	37
10	58	163	20	12.6	14.1	9.5	114	645	4.7	40
11	58	163	20	12.8	13.4	9.9	113	637	4.5	42
12	58	163	20	12.7	13.0	9.6	110	612	4.3	36
13	58	165	30	12.6	13.5	9.7	112	628	4.6	37
14	58	168	19	12.5	14.1	9.6	113	637	4.5	33
15	58	173	28	12.8	13.3	9.5	111	620	4.6	36
16	58	178	23	12.4	12.8	10.4	106	595	4.7	45
17	58	178	24	11.8	13.3	10.5	106	595	4.8	51
18	58	180	24	12.5	13.0	9.5	109	608	4.1	38
19	59	157	22	12.3	13.2	9.6	111	620	4.5	44
20	59	160	24	12.4	13.3	9.8	111	620	4.6	46
21	59	163	22	12.1	13.8	9.7	111	620	4.7	41
22	59	165	23	13.5	13.9	9.7	114	645	4.7	32
23	59	165	25	11.5	13.5	9.5	110	612	4.5	48
24	59	165	29	12.6	13.6	9.6	112	628	4.4	40
25	59	168	24	12.6	13.7	9.4	112	628	4.6	41
26	59	168	26	12.8	13.8	9.7	113	637	4.7	40
27	59	170	23	13.6	13.0	9.9	114	645	4.8	40
28	59	170	23	12.7	14.1	9.7	114	645	4.4	54
29	59	170	30	12.8	13.5	9.8	113	637	4.7	47
30	59	173	24	12.7	13.6	9.8	113	637	4.3	40
31	59	173	27	12.9	13.4	9.8	113	637	4.4	41
32	59	173	28	12.7	13.9	9.9	113	637	4.6	40
33	59	173	28	12.7	13.9	10.3	114	645	4.6	38
34	59	175	19	12.9	12.6	10.1	113	637	4.8	42
35	59	175	21	12.8	13.6	9.8	113	637	4.7	44
36	59	175	27	12.7	12.9	10.3	113	637	4.5	44
37	59	175	30	12.8	13.5	9.7	112	628	4.6	54
38	59	178	22	12.3	13.5	9.8	112	628	4.6	48
39	59	178	27	12.5	13.7	9.9	112	628	4.8	48
40	59	178	30	14.0	12.7	9.1	113	637	4.5	29
41	60	175	23	12.7	13.7	10.1	112	628	4.7	48
42	61	160	20	12.7	13.0	9.9	111	620	4.4	47
43	61	160	26	11.9	13.6	10.2	111	620	4.6	37
44	61	163	25	10.1	12.4	10.2	104	582	4.4	47
45	61	165	24	12.6	12.9	10.6	111	620	4.4	39
46	61	168	19	12.8	14.0	10.6	114	645	4.7	31
47	61	168	26	12.2	12.9	10.4	110	612	4.6	34
48	61	168	28	11.7	13.3	10.3	110	612	4.7	48
49	61	168	30	12.5	13.7	10.6	112	628	4.6	31
50	61	170	23	11.4	13.6	10.5	112	628	4.8	43
51	61	170	28	12.7	14.1	10.2	114	645	4.4	38
52	61	173	20	12.1	13.7	10.5	112	628	4.4	50
53	61	173	22	13.3	13.5	10.9	114	645	4.8	35
54	61	173	23	13.2	14.2	10.3	115	653	4.7	34
55	61	173	24	11.6	13.3	10.3	112	628	4.3	34
56	61	175	19	11.3	14.1	10.4	112	628	4.8	41
57	61	175	22	10.6	14.0	10.4	111	620	4.5	56
58	61	175	22	11.2	14.0	10.2	112	628	4.6	56
59	61	175	23	11.8	13.6	10.5	112	628	4.9	50
60	61	175	27	12.0	14.2	10.2	113	637	4.3	51
61	61	178	20	12.4	13.5	10.8	113	637	4.7	54
62	61	178	21	11.6	14.0	10.2	112	628	4.6	38
63	61	178	23	12.0	13.8	10.3	112	628	4.8	40
64	61	178	30	12.4	14.0	10.7	113	637	4.6	51
65	61	180	23	12.8	14.3	10.5	113	637	4.1	58
66	61	180	24	12.1	13.5	10.3	112	628	4.1	30
67	61	180	30	11.8	13.7	10.2	111	620	4.5	34
68	62	157	25	13.7	12.0	9.4	112	628	4.6	26
69	62	163	26	12.9	14.1	10.4	114	645	4.3	40
70	62	168	22	11.5	14.2	10.1	113	637	4.7	49
71	62	168	25	13.2	14.3	10.1	116	662	4.4	46
72	62	168	28	13.1	13.7	10.4	115	653	4.9	32
73	62	170	26	11.4	13.8	10.5	112	628	4.3	43
74	62	173	19	11.7	14.1	10.4	113	637	4.7	53
75	62	175	24	12.6	14.2	9.8	114	645	4.5	36
76	62	178	22	11.8	14.1	10.3	113	637	4.5	48

TABLE 8.—Teleroentgen Measurements of 277 Normal Hearts of Soldiers—(*Continued*)

No.	Wt., Kg.	Height, Cm.	Age	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Volume, C.c.	Arch, Cm.	Angle, Degrees
77	62	178	23	12.2	14.0	9.7	114	645	4.6	37
78	62	178	28	11.1	13.5	9.8	112	628	4.1	48
79	62	178	29	12.6	13.8	9.7	113	637	4.7	45
80	63	155	26	11.3	13.4	10.3	112	628	4.8	53
81	63	160	30	11.8	13.5	10.4	112	628	4.7	55
82	63	163	27	11.4	13.5	10.2	112	628	4.6	45
83	63	166	23	12.1	13.6	10.1	113	637	4.3	25
84	63	168	26	11.8	13.2	10.0	112	628	4.0	41
85	63	170	22	11.5	13.8	9.9	112	628	4.5	40
86	63	170	22	13.6	13.0	9.6	113	637	4.7	32
87	63	170	23	11.7	13.9	10.1	113	637	4.3	42
88	63	170	24	11.7	13.5	10.4	113	637	4.9	54
89	63	173	20	13.2	14.2	10.4	115	653	4.9	32
90	63	173	22	11.2	14.4	10.2	114	645	4.7	50
91	63	173	23	11.6	14.5	10.1	114	645	4.7	48
92	63	173	23	11.8	13.6	10.1	114	645	4.6	34
93	63	173	25	11.5	13.9	10.4	114	645	4.4	48
94	63	173	25	12.0	13.9	10.4	114	645	4.4	34
95	63	173	26	12.7	13.8	10.2	114	645	4.5	34
96	63	173	28	12.0	14.1	10.2	114	645	4.5	41
97	63	175	22	10.6	14.4	10.4	114	645	4.7	54
98	63	175	27	11.1	14.5	10.7	115	653	4.3	55
99	63	175	27	11.4	13.7	10.5	113	637	4.6	42
100	63	178	19	11.0	13.9	10.6	113	637	4.3	44
101	63	178	22	12.2	13.8	10.5	114	645	4.7	31
102	63	178	24	11.1	13.6	10.1	112	628	4.4	50
103	63	178	25	12.9	13.9	10.4	114	645	4.9	40
104	63	178	27	12.0	14.2	10.5	114	645	4.5	45
105	63	178	28	12.1	13.9	10.7	114	645	4.0	58
106	64	168	20	11.7	14.0	10.4	114	645	4.8	40
107	64	168	22	12.6	13.9	10.4	114	645	4.6	37
108	64	170	21	12.3	13.8	10.5	114	645	4.5	33
109	64	170	23	11.7	14.6	10.6	114	645	4.8	50
110	64	170	24	12.6	14.6	10.6	116	662	4.8	46
111	64	173	21	12.4	13.8	10.6	114	645	4.4	43
112	64	173	24	12.0	14.8	10.6	115	653	4.5	56
113	64	175	22	12.7	14.8	10.8	116	662	4.6	56
114	64	175	26	12.6	14.4	10.7	115	653	4.9	35
115	64	175	26	12.4	14.6	10.5	115	653	4.4	35
116	64	178	23	12.8	13.8	10.7	115	653	4.6	48
117	64	178	25	12.4	14.5	10.4	116	662	4.7	45
118	64	178	25	13.1	14.4	10.6	116	662	4.8	45
119	64	178	26	12.3	14.7	10.7	115	653	4.3	50
120	64	180	23	13.7	14.3	10.7	117	671	4.7	40
121	64	180	26	13.5	14.4	10.3	117	671	4.5	37
122	64	189	27	13.3	14.3	10.4	116	662	4.6	31
123	65	165	22	12.6	13.8	10.8	115	653	4.4	36
124	65	168	23	13.2	13.4	10.7	115	653	4.5	34
125	65	168	27	13.2	14.0	10.0	116	662	4.9	32
126	65	170	22	12.8	13.9	10.8	115	653	4.3	35
127	65	173	19	13.1	13.7	10.9	116	662	4.6	46
128	65	173	25	12.6	13.4	10.8	115	653	5.0	38
129	65	173	26	13.4	13.9	10.6	116	662	4.6	43
130	65	175	20	12.5	13.9	11.0	116	662	4.7	53
131	65	175	26	13.0	13.8	10.8	116	662	4.7	43
132	65	178	26	12.9	14.1	10.8	117	671	4.8	39
133	65	180	23	11.4	14.0	11.2	115	653	4.4	54
134	65	180	27	13.3	13.9	10.6	117	671	4.6	55
135	65	184	23	12.7	14.3	10.9	117	671	4.7	40
136	65	184	28	12.8	14.1	10.3	116	662	4.6	47
137	66	170	28	13.7	13.5	10.5	116	662	4.5	54
138	66	178	23	12.9	13.8	10.6	116	662	4.4	45
139	66	178	26	12.2	14.3	10.3	117	671	4.5	55
140	66	180	26	13.6	13.9	10.5	116	662	4.5	29
141	67	160	22	12.9	13.7	10.7	116	662	4.5	38
142	67	168	24	13.4	14.0	10.5	117	671	3.8	34
143	67	168	26	13.6	13.8	10.6	117	671	4.7	33
144	67	168	29	12.8	14.0	10.2	118	679	4.5	40
145	67	170	26	13.6	14.1	11.2	121	705	4.6	32
146	67	170	28	13.6	14.2	10.6	119	688	4.7	34
147	67	173	29	12.9	15.0	11.2	123	723	4.8	49
148	67	178	21	13.6	14.7	10.8	122	723	4.6	42
149	67	178	22	12.9	14.5	10.3	121	705	4.6	44
150	67	178	23	13.5	13.9	10.4	119	688	4.7	45
151	67	178	31	13.0	13.9	10.7	119	688	4.6	44
152	67	180	24	13.4	14.3	10.8	122	714	4.6	41

TABLE 8.—TELEROENTGEN MEASUREMENTS OF 277 NORMAL HEARTS OF SOLDIERS—(*Continued*)

No.	Wt., Kg.	Height, Cm.	Age	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Volume, C.c.	Arch, Cm.	Angle, Degrees
153	67	180	27	12.1	15.0	10.1	121	705	4.5	58
154	67	183	31	13.6	14.1	10.4	121	705	4.6	36
155	68	165	22	13.0	13.9	10.6	119	688	4.9	48
156	68	168	26	13.9	14.1	9.7	121	705	4.7	33
157	68	170	20	13.3	14.2	10.6	122	714	4.4	39
158	68	170	22	13.4	14.0	10.4	122	714	4.8	45
159	68	173	18	13.8	14.3	10.8	123	723	4.9	33
160	68	172	22	13.5	13.9	10.7	120	697	4.4	30
161	68	173	25	13.4	14.5	10.4	123	723	4.2	46
162	68	173	25	13.6	14.2	10.8	123	723	4.7	51
163	68	173	29	12.7	14.0	10.2	120	697	4.7	40
164	68	175	25	11.9	14.3	10.8	118	679	4.3	52
165	68	175	26	13.3	13.8	10.7	121	705	5.1	47
166	68	175	26	12.7	14.2	10.8	121	705	4.6	48
167	68	178	24	13.7	14.6	11.2	125	741	4.7	47
168	68	178	27	13.4	14.5	10.0	123	723	4.6	45
169	68	178	29	13.4	14.3	10.8	124	732	4.5	52
170	68	178	29	13.6	14.4	11.2	125	741	4.9	47
171	68	180	20	13.4	14.1	10.6	123	723	4.7	57
172	68	184	28	13.6	14.7	10.9	125	741	5.0	46
173	68	183	40	13.6	14.0	10.5	123	723	4.3	41
174	69	168	27	13.5	14.7	10.6	125	741	5.1	47
175	69	168	31	13.6	14.2	10.3	123	723	5.0	37
176	69	170	21	12.9	14.1	10.3	122	714	4.5	37
177	69	170	26	13.5	14.1	10.2	123	723	4.6	29
178	69	173	29	13.6	14.3	10.8	124	732	4.6	45
179	69	175	20	12.7	14.7	10.4	122	714	5.1	35
180	69	178	21	13.5	14.6	10.8	124	732	4.7	38
181	69	178	24	11.4	14.6	9.9	119	688	4.2	54
182	69	180	23	12.9	14.4	10.5	123	723	4.3	34
183	69	180	26	13.1	14.4	10.9	124	732	4.4	36
184	70	168	27	13.5	14.4	10.3	124	732	4.8	43
185	70	170	22	13.5	14.7	10.4	125	741	4.5	40
186	70	173	22	13.5	14.9	10.2	126	750	4.4	44
187	70	175	23	13.5	13.8	11.2	124	732	4.4	49
188	70	175	24	13.4	14.5	10.5	125	741	4.7	33
189	70	175	25	13.5	14.6	10.4	125	741	4.5	39
190	70	175	28	13.4	14.4	10.6	125	741	4.6	50
191	70	175	28	13.5	14.6	10.3	125	741	4.8	30
192	70	175	28	13.6	14.8	10.5	127	759	4.6	52
193	70	178	22	13.4	14.6	10.8	125	741	4.7	40
194	70	178	23	13.3	14.7	10.8	126	750	4.9	42
195	70	178	23	13.6	13.9	11.2	124	732	5.0	52
196	70	178	25	13.4	15.0	10.2	127	759	4.4	57
197	70	178	31	13.4	13.8	10.5	122	714	4.8	41
198	70	178	34	13.3	14.4	10.4	123	735	5.0	47
199	71	168	24	13.5	14.2	11.3	126	750	5.1	49
200	71	170	27	13.4	14.4	10.3	126	750	4.9	49
201	71	170	27	13.7	14.0	10.0	123	750	4.8	27
202	71	173	26	11.6	14.3	11.0	122	714	4.5	63
203	71	173	29	13.5	14.9	10.4	127	759	4.7	36
204	71	175	21	12.9	15.1	10.1	127	759	4.2	62
205	71	175	26	13.3	14.3	10.5	125	741	4.5	53
206	71	175	32	13.4	14.6	10.5	126	750	4.4	48
207	71	178	27	13.4	14.7	10.8	127	759	4.8	56
208	71	178	28	13.6	15.2	11.1	129	777	5.0	40
209	71	178	29	13.4	15.2	11.2	128	768	4.6	43
210	71	178	30	13.3	14.8	10.4	127	759	4.6	54
211	71	180	28	13.4	14.6	10.6	127	759	4.6	43
212	71	183	19	13.3	14.3	10.5	126	750	4.8	35
213	72	168	30	13.4	14.8	10.2	127	759	4.9	47
214	72	170	26	13.8	14.3	10.2	127	759	4.5	28
215	72	173	24	13.5	14.5	10.4	127	759	4.6	44
216	72	173	28	13.4	14.2	10.4	126	750	4.7	34
217	72	175	21	13.7	14.1	10.2	127	759	4.9	37
218	72	175	24	13.5	14.8	11.1	128	768	4.5	33
219	72	180	29	13.3	14.9	10.5	128	768	4.5	42
220	72	180	31	13.6	15.0	10.4	129	777	4.6	47
221	72	183	25	13.5	15.2	11.3	130	786	4.5	45
222	72	184	25	13.8	14.6	10.4	130	786	4.6	42
223	73	170	26	13.7	14.7	10.6	130	786	4.9	41
224	73	170	32	14.2	14.3	10.3	130	786	5.2	23
225	73	175	25	13.5	14.7	10.1	129	777	4.7	50
226	73	178	26	13.4	14.5	10.4	128	768	4.7	35
227	73	183	30	13.5	15.1	9.9	129	777	4.7	41
228	74	178	23	13.7	15.2	10.4	130	786	4.5	36

TABLE 8.—Teleroentgen Measurements of 277 Normal Hearts of Soldiers—(*Continued*)

No.	Wt., Kg.	Height, Cm.	Age	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Volume, C.c.	Arch, Cm.	Angle, Degrees
229	74	178	28	13.5	14.9	10.3	129	777	5.2	48
230	74	180	24	13.8	14.8	10.3	130	786	4.8	36
231	74	180	27	13.8	14.7	10.5	130	786	4.6	52
232	74	180	30	13.9	14.8	10.3	130	786	4.5	34
233	74	183	31	13.8	15.1	9.9	130	786	4.7	44
234	75	165	21	13.7	14.7	10.4	130	786	4.7	42
235	75	168	23	13.9	14.1	10.2	129	777	4.6	29
236	75	173	28	13.7	14.3	10.4	130	786	5.0	33
237	75	173	29	13.6	14.5	10.6	130	786	4.8	42
238	75	178	24	13.5	14.5	10.8	130	786	4.6	54
239	75	178	24	13.9	14.3	10.7	131	795	4.9	27
240	75	180	24	13.5	14.3	10.5	129	777	4.2	42
241	75	180	29	13.5	14.9	10.6	130	786	4.6	32
242	75	180	29	13.6	14.5	10.6	130	786	4.2	37
243	75	180	30	13.8	14.6	10.5	130	786	5.0	35
244	75	180	31	13.7	14.2	10.9	130	786	4.9	36
245	75	184	27	13.6	14.4	10.7	130	786	4.7	42
246	75	184	28	13.5	14.8	10.8	131	795	4.8	44
247	76	168	23	13.7	14.9	10.8	132	804	4.4	37
248	76	173	23	13.6	14.6	10.7	131	795	5.1	34
249	76	178	23	13.4	14.9	10.6	131	795	4.6	49
250	76	178	31	13.5	13.9	10.8	129	777	4.5	41
251	76	180	23	13.8	14.5	11.3	133	813	4.4	44
252	76	180	29	13.7	14.7	10.8	132	804	4.6	50
253	76	180	29	13.7	15.0	10.8	133	813	4.6	50
254	76	184	23	13.6	14.7	10.8	132	804	5.0	47
255	77	165	22	14.3	14.5	10.3	133	813	4.9	24
256	77	168	26	13.7	14.9	10.9	133	813	4.9	34
257	77	173	25	13.8	14.0	10.5	131	795	4.5	34
258	77	173	28	13.4	14.7	10.7	132	804	4.5	38
259	77	175	25	13.8	14.5	11.3	133	813	4.9	34
260	77	178	24	13.7	14.5	10.9	132	804	4.8	43
261	77	178	27	13.6	14.3	10.0	130	786	4.4	38
262	77	180	27	13.4	14.9	10.8	132	804	4.5	47
263	78	173	26	14.0	12.8	10.1	132	804	4.7	28
264	78	178	27	13.5	15.0	10.6	133	813	4.5	56
265	79	170	25	13.7	15.2	10.8	135	832	5.0	39
266	79	178	29	14.2	14.9	9.9	136	841	4.5	34
267	79	183	25	13.2	14.5	11.6	132	804	4.6	57
268	79	184	25	13.5	14.0	10.7	129	777	4.2	38
269	80	178	25	13.9	15.2	11.1	135	822	4.4	50
270	80	180	30	13.5	14.6	11.3	134	823	5.1	46
271	81	165	26	13.5	14.9	11.2	135	832	4.7	32
272	81	178	28	14.3	13.9	10.3	134	823	4.8	26
273	81	180	30	13.2	14.5	10.8	134	823	4.6	48
274	82	173	25	13.5	14.8	10.7	134	823	4.5	41
275	83	178	25	13.8	14.5	10.9	135	832	5.0	32
276	83	178	29	13.6	15.1	10.9	136	841	4.4	36
277	84	184	38	13.7	14.9	11.4	137	850	4.5	46

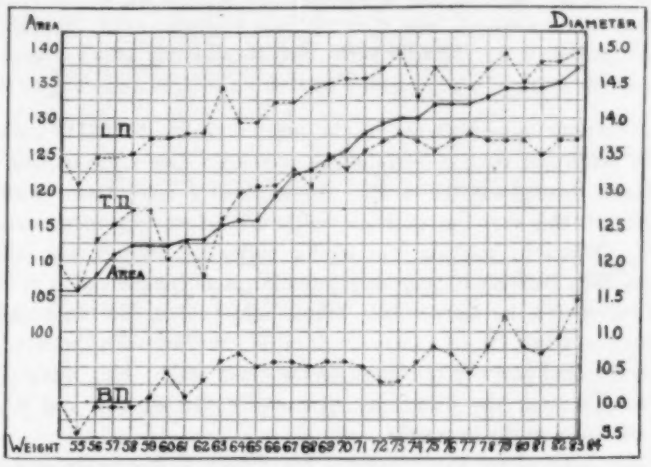
occupying a more median position in the chest, was present in 2.0 per cent. of the men. In these men the angle measured 54, 55, 56, 60 and 63 degrees, respectively.

No evidence has been found in this study that the hearts of soldiers are enlarged after active military service. The average measurements for the diameters and area agree closely with the normal figures of Dietlen and Bardeen.

The individual measurements for area are well within the normal range.

The individual measurements for the transverse diameter, in cases with the same body weight, show considerable variation, and emphasize the danger of basing an opinion of size on the determination of this diameter alone.

A consideration of the shape of the heart is important in any questionable enlargement. If the area is not measured, the angle formed by the transverse and long diameters can be an aid.



Relation of area and diameters of heart to body weight. T.D. = transverse diameter; L.D. = long diameter; B.D. = broad diameter.

Hearts of soldiers who have performed active service are largely of the broad type, with a wide transverse diameter. Only a small percentage of the men had hearts of the narrow type, with a small transverse diameter and a broad angle.

TELEROENTGEN ESTIMATIONS OF HEART SIZE IN CASES OF EFFORT SYNDROME*

BERTNARD SMITH, M.D.

LOS ANGELES

Silhouette measurements of the heart were made in 119 cases of effort syndrome by the teleroentgen method. The same technic was followed throughout the work. All exposures were taken with the subject in the standing position, with the target 6½ feet from the plate. When in position, facing the plate, the subject was told to take a deep breath and then empty his lungs as completely as possible. Following this, he took a half breath and held it for the exposure, which was from 1½ to 4 seconds' duration, varying with the weight of the individual and the thickness of the chest wall. This method was adopted because the directions were easily carried out, and it gave satisfactorily uniform results.

From the plates thus obtained the following measurements were made:

1. Ml.: Maximum left border.
2. Mr.: Maximum right border.
   From the sum of these was obtained the maximum transverse diameter T.D.
3. L.D.: Maximum long diameter from the right auricular notch to the most distant apical border.
4. B.D.: Maximum broad diameter, measured at right angles from L.D. to the most distant borders.
5. The angle formed by the long and transverse diameters.
6. The diameter of the aortic arch.
7. The parallel ray silhouette area[1] was obtained by the planimetric method and from this was calculated the volume by the Bardeen formula.[2]

In the cases studied, the men who gave a history of symptoms present before entering the army showed a lower general strength and a poorer physical development than did those patients whose symptoms developed during active military duty. The cases are tabulated in this report into two groups, according to the time of onset of the general effort syndrome symptoms.

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* Report from Studies made on the Cardiovascular Service, U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Bardeen, C. R.: Am. J. Roentgenol. **4**:604, 1917.
2. Bardeen, C. R.: Am. J. Anat. **23**:423, 1918.

1. CASES WITH SYMPTOMS BEFORE MILITARY SERVICE

The sixty-nine cases of this group are arranged in Table 1 by weight. Bardeen [2] has stated that the transverse diameter is about 7.0 per cent. less in the standing than in the recumbent position, and about half of this difference is found between the sitting and recumbent positions. These differences have been taken into consideration in comparing measurements with the Dietlen and Bardeen tables for normals.

TABLE 1.—HEART MEASUREMENTS IN CASES OF EFFORT SYNDROME WITH SYMPTOMS PRESENT BEFORE MILITARY SERVICE

Weight, Kg.	Cases	Height, Aver., Cm.	Age, Average	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Angle, Degrees		Arch, Cm.
								Range	Aver.	
45-49	2	171	28	8.8	13.2	8.9	90	60-65	62.5	4.1
50-54	8	171	25	9.9	13.3	9.0	107	41-63	53.0	4.5
55-59	18	172	24	10.8	13.5	9.2	111	30-65	47.0	4.5
60-64	22	171	27	12.2	13.2	9.5	112	32-61	44.5	4.5
65-69	13	174	26	12.1	13.5	9.6	113	36-58	45.1	4.6
70-74	4	174	25	12.4	14.3	9.7	122	28-60	47.8	4.6
75-84	2	176	23	11.2	14.7	9.7	123	41-59	43.0	4.4

When the measurements for the transverse diameters are compared with the Dietlen [3] and Bardeen [4] tables for normals, the effort syndrome cases give an average diameter that is 0.68 cm. less than the normal average. Meakins and Gunson [5] have reported measurements by the orthodiagraphic method of fifty cases in which they found the transverse diameter averaged 0.70 per cent. less than the normal as given in Dietlen's tables. When the heart volume is compared with the Bardeen table, the effort syndrome cases give an average that is 9.8 per cent. less than the normal, when arranged according to the subject's weight.

Measurements were made on 277 men who had had at least three months active duty in the fighting line, and who had gone through their training and forced marches without symptoms. The full report is reserved for a separate publication, but a summary of the measurements is given in Table 2 for comparison, since the technic followed was the same as with the cases in this report.

When the measurements for the effort syndrome cases are compared with this series of normal hearts, the transverse diameters for the sixty-nine patients average 0.98 cm. less. However, when the volumes are compared, the average difference for the effort syndrome cases is 10.1 per cent. less, as arranged by weight, than for the men who had performed full duty.

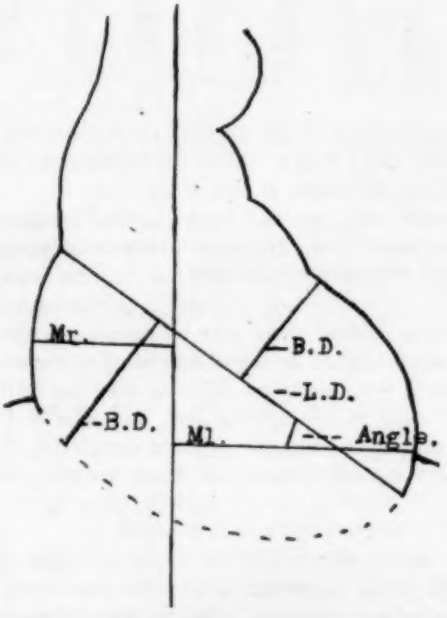
3. Dietlen, H.: Deutsch. Arch. f. klin. Med. **88**:55, 1907.
4. U. S. Army X-Ray Manual.
5. Meakins, J. C., and Gunson, E. B.: Heart **7**:1, 1918.

TABLE 2.—Heart Measurements of Soldiers after Military Service

Weight, Kg.	Cases*	Height, Aver., Cm.	Age, Average	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Angle, Degrees	
								Range	Average
55-59	40	170	25	12.6	13.4	9.9	111	29-60	41
60-64	82	168	24	11.9	13.6	10.2	113	28-56	43
65-69	61	178	27	11.5	14.1	10.6	118	26-57	41
70-74	50	177	27	13.4	14.7	10.7	127	24-63	42
75-79	35	176	27	13.7	14.5	10.6	129	24-56	41
80-84	9	179	29	13.7	14.7	10.9	135	26-50	40

* These men were orthopedic cases in U. S. Army General Hospital No. 9.

The silhouette of the long, narrow heart was found in 24.6 per cent. of the sixty-nine cases. This does not include the rounded, flask shaped shadow with a small transverse diameter. The low, broad type of shadow was found in 29.0 per cent. of the cases. The angle formed by the long and transverse diameters is small in the low, broad heart



and widens as the type approaches the narrow form. In Table 1 are given the range and average of this angle for the different weight groups. For the sixty-nine cases the range is from 30 to 65 degrees, with a total average of 49.6 degrees. The range of this angle for the narrow types of hearts is from 52 to 65 degrees, with an average of 57.6 degrees.

The majority of the sixty-nine cases were of the type of chronic physical invalidism,[6] and had a low weight. If the weights are compared with the normal figures for the same age and height we obtain the following:

Weight 45-49 average 25.4 per cent. below normal
Weight 50-54 average 17.0 per cent. below normal
Weight 55-59 average 18.6 per cent. below normal
Weight 60-64 average 4.1 per cent. below normal
Weight 65-69 average 1.0 per cent. below normal
Weight 70-74 average 1.1 per cent. above normal
Weight 75-84 average 1.7 per cent. above normal

Of the sixty-nine patients, 65 per cent. were below their normal weight, as given in the standard tables for age and height. This low weight in these men was associated with poor skeletal strength that had persisted for a number of years and often since childhood. Bardeen[7] states that "the size of the heart is determined rather by the development of the skeletal musculature than mere body weight, although the latter alone is subject to direct measurement." If the small heart of the effort syndrome is part of the picture of poor muscular development, later statistics will be of interest from those patients who have been developed to take up more active civil work.

TABLE 3.—HEART MEASUREMENTS IN CASES OF EFFORT SYNDROME WITH SYMPTOMS DEVELOPING DURING MILITARY SERVICE

Weight, Kg.	Cases	Height, Aver., Cm.	Age, Average	T. D., Cm.	L. D., Cm.	B. D., Cm.	Area, Sq. Cm.	Angle, Degrees		Arch, Cm.
								Range	Aver.	
50-54	4	162	23	11.1	12.8	9.6	107	43-61	48.8	4.2
55-59	7	174	24	10.9	13.3	9.6	109	30-54	45.8	4.5
60-64	15	171	24	11.7	13.9	9.7	112	31-48	43.5	4.5
65-69	13	174	25	12.5	13.7	9.8	118	27-56	42.7	4.7
70-74	11	172	26	12.7	14.3	10.4	124	34-61	41.9	4.9

2. CASES DEVELOPING SYMPTOMS DURING MILITARY SERVICE

No cases are included in this report in whom effort syndrome symptoms developed after an infectious disease. Measurements from fifty cases, in which the symptoms were of recent origin, are given in Table 3 as grouped by weight. The transverse diameters have a total average difference of 0.28 cm. when compared with the Dietlen and Bardeen tables. The volume average is 2.1 per cent. less than the Bardeen figures for normal when arranged by weight. When the fifty cases are compared with the normals of Table 2, the transverse diameters of the effort syndrome cases have an average that is 0.54 cm. less and an average volume that is 2.7 per cent. below the average for

6. Campbell, C. M.: J. A. M. A. **71**:1621 (Nov. 16) 1918.
7. Bardeen, C. R.: Anat. Rec. **10**:176, 1915.

the normals. The long, narrow type of heart shadow is found in only 2.0 per cent. of the cases with recent onset of symptoms, while the broad heart is seen in 50 per cent. The range for the angle in this group is from 27 to 61 degrees, with an average of 44.7 degrees for the fifty cases.

A comparison of the weights of the men in this group with the normal figures for height and age gives an equally sharp contrast to those of Group 1.

Weight 50-54	average	6.0 per cent.	below normal
Weight 55-59	average	10.0 per cent.	below normal
Weight 60-64	average	11.6 per cent.	above normal
Weight 65-69	average	0.6 per cent.	above normal
Weight 70-74	average	7.4 per cent.	above normal

The weights range from 88 to 109 in per cent. of normal, with a total average for the 50 cases of 102.3 per cent.

SUMMARY

Cases of effort syndrome, in which symptoms have persisted for a long period of time, have smaller hearts than normal when compared by measurements of the transverse diameter, area and volume.

The narrow, long heart, or "drop-heart," is not the predominant type found. The small heart may vary in form as widely as the normal, and usually shows a decrease in the transverse, long and broad diameters.

The smaller measurements are found in those men whose skeletal musculature has never been developed normally.

The patients studied at Lakewood, who acquired the effort syndrome during active army duty, show silhouette measurements that are well within the normal range for area and volume. The transverse diameters average slightly less than normal. In such hearts the long diameter is usually slightly increased.

The angle formed by the transverse and long diameters shows a greater average width in the men whose symptoms have been of long duration than in the normals and in the cases with a more recent onset. Those individuals, whose silhouette gave this wide angle, had also a long, narrow chest wall.

I wish to express my indebtedness to Lieut. F. W. Keyes for his assistance in constructing the apparatus for the teleroentgen studies, and to Lieut. Milton H. Glover for his cooperation in the roentgen-ray technic.

PURULENT TYPHOID MENINGITIS

REPORT OF A CASE

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HALSTEAD, KAN.

Meningitis due to the *B. typhosus* is a relatively rare disease. Cole collected the cases recorded up to 1904. We have been able to find twenty-three cases recorded in the literature since that time.

In addition to reviewing the cases reported by Cole, we wish to report a case in which cholecystitis and otitis media were additional complications. We had the opportunity of doing a necropsy in this case, thus making an anatomic study of the complications possible. The findings of the meningeal complication and of a pure typhoid culture comply with all of Cole's requirements for the diagnosis of purulent meningitis.

REPORT OF CASE

CASE 3494.—R. A., aged 6, admitted to the Halstead Hospital, Oct. 12, 1919, with complaint of headache, fever and abdominal pain.

Family History.—Negative. One brother living and well. The brother later developed typhoid fever and was a patient in the hospital. Positive Widal; no complications.

Personal History.—When 3 years old, the patient had swollen glands on both sides of neck, not associated with pain or redness, but tender. These swellings disappeared in about four weeks. Patient had an acute tonsillitis when 5 years of age.

Present History.—The patient had an attack of diarrhea, October 6. On the afternoon of the seventh, he complained of abdominal pain. Two days later he was seen by a physician. On the second day the patient's temperature was 102 F. October 12, it was 105 F.

The boy was brought to the hospital the evening of October 12. He was seen for the first time by our staff. His temperature was 105.8, pulse 150, leukocyte count 9,000. His head, neck and chest were negative. His abdomen was somewhat distended and tender. The spleen was not definitely palpable, nor were any other masses found. There was painful urination. The urine was slightly clouded, and showed a trace of albumin; otherwise it was negative.

During the night he was restless, thirsty, expelled much flatus and several watery stools, with mucus. The next day the patient was delirious, the temperature remaining above 104 F.; the pulse rate was about 120. On the following three days, he was quite restless, at times passing urine and feces involuntarily. He was delirious and picked at the bed clothes. At times he was noisy, complained of stiffness of his legs, pain in his throat and difficult deglutition. His temperature slowly came down. The spleen was now definitely palpable, but at no time were rose spots noted.

On the sixth day his temperature reached 101 F. He had some epistaxis on this day and later passed several dark red stools which showed blood. He seemed more quiet and rational, but complained of pain on voiding urine and when his bowels moved. During the following days his temperature remained between 100 F. and 102 F.; pulse, 104 to 130. On the eleventh day,

the temperature again rose to 104 F.; pulse was about the same. Voiding and passing of stools was painful; the patient was restless and crying. A mass, soft and fluctuating, had been noticed in the right subcostal region two days earlier. This had increased until it reached the level of the umbilicus and was plainly visible. The leukocytes numbered 17,400.

Diagnosis.—Acute cholecystitis was diagnosed.

Operation.—In the afternoon an operation was performed. The gallbladder was very much enlarged, extending below the umbilicus; its vessels were congested, walls thin and almost transparent. About 70 c.c. of a rather thin, slimy, greenish bile was evacuated, and then a greenish yellow fluid was found. Smears showed only a very few epithelial-like cells. The culture was negative.

Subsequent Course.—During the next three days, the temperature ranged from 103 to 104.5 F.; pulse, 120 to 134. The patient was restless, crying and very thirsty. On the sixteenth day, his neck was stiff and the head was drawn back. There was involuntary passage of urine and stools. The throat contained much phlegm. A yellowish discharge came from the left ear. The pulse ranged between 116 and 132. On the evening of the seventeenth day, at 6 p. m., the patient had a convulsion, lasting about twenty-five minutes, during which the temperature rose to 107 F., pulse to 140. The pupils were markedly dilated. The patient was cyanotic.

The next day the patient was restless; the muscles of the face were twitching, temperature 103 to 106 F.; pulse, 120 to 150; neck stiff; Kernig positive, knee jerks somewhat increased. Spinal puncture showed fluid under pressure, cloudy; about 15 c.c. was removed. Cell count, 400, mostly mononuclears. Smear: gram-negative, short bacilli, slightly motile; mononuclear cells. Culture; motile bacilli, gram-negative.

On the eighteenth day, the patient was quieter; cyanotic; temperature, 105 to 105.5 F.; pulse weak, 140 to 156, but difficult to count; blood tinged mucus in throat.

Patient died at 2 p. m.

A spinal puncture at 2:30 p. m. showed fluid not under increased pressure, turbid, about 15 c.c. Cell count, 400, mostly mononuclears. Smear: gram-negative, short bacilli; Ross Jones slightly positive. Culture: hanging drop, motile bacilli, gram-negative.

Necropsy.—Four p. m. Body, that of a white boy, about 5 or 6 years old, fairly good build, nutrition fair, small bruises over left internal malleolus, and external surface right ankle. Operation wound with rubber tube drain in upper right abdomen. Pupils, 3 mm.; equal.

Brain: Meninges somewhat injected; on removing dura brain surface of frontal lobe covered with thin, pale yellow, cloudy film (Figs. 1 and 2). A collection of pus (?) in posterior fossa between cerebellum and medulla.

Abdomen: No free fluid in abdomen. Omentum well walled about gallbladder region.

Stomach and Intestines: About 36 inches below pylorus, a short intussusception, of about 2 inches, existed. Below this, a large amount of tarry stool filled about 2 feet of the intestine. On section, no ulcers observed, except near ileocecal valve, where the mucosa was markedly reddened, and studded with minute ulcerations. Lymph nodes in mesentery, especially near intestine, are markedly enlarged, measuring 1 cm. and more in length and from 0.5 to 0.7 c.c. in thickness.

Liver and gallbladder appeared to be quite normal. Gallbladder shrunk to about 6 cm. in length and in diameter to the size of the rubber tube drain placed at operation. Wall not thickened. Liver on section normal. Cystic and common duct appear normal in size and structure; no obstruction present.

Spleen: Increased in size 10.5 by 8.5 by 4, weight, 146 gm. Splenic nodules show prominently in section.

Kidneys: Fatty capsule, comparatively thin; capsule strips easily from both. Left kidney, 10 by 6.5 by 4.5, weight, 163 gm. Right kidney, 9 by 5 by 3, weight, 84 gm. Cortex about from 5 to 8 mm. thick in both kidneys. Pelves both markedly dilated as are the ureters at the lower end. Both stood out prominently, measuring about 8 or 10 mm. diameter from pelvic brim to the bladder. Probe passed easily to the bladder.

Heart and Lungs: Not taken.

Microscopical: Brain shows meninges (except dura) markedly infiltrated with polymorphonuclear leukocytes and other cells (Fig. 3). This infiltration follows the vessels only a short distance into the cortex.

On closer examination it is seen that many of the cells in the meninges are not polymorphic cells but large plasmalike cells, some about 15 microns in diameter, markedly vacuolated, with small reddish stained inclusion particles, possibly red cells, the nuclei more or less eccentrically placed, rather

Fig. 1.—Photograph of left surface of brain.

large, irregular shaped, with a small amount of chromatin material. These cells are not numerous (Fig. 4).

What is particularly striking in a cursory examination is that the cellular infiltration about the blood vessels is markedly less dense than elsewhere; this is especially true of the veins (Fig. 3). The mononuclear cells are about equally distributed in the perivascular areas and elsewhere. In the densely cellular areas are numerous small nuclear bodies from 3 to 4 microns in diameter, quite uniformly stained, with no darker stained chromatin masses.

The most common cells besides the polymorphonuclears are plasma-like, with pale staining, more or less vacuolated cytoplasm. The nuclei are large, round, eccentric in position, usually one or two nucleoli, and very little other chromatin.

There is remarkably little perivascular infiltration in the cortex, and a surprising decrease about the blood vessels in the membranes.

The area at the base of the cerebellum, which in gross appeared as pus, showed cellular infiltration as described above. Despite a careful search, no definite bacilli could be found in 10 micron sections.

Kidneys: Markedly dilated convoluted tubules; capillaries congested in cortex, glomeruli only slightly enlarged. Convoluted tubules show granular epithelium, nuclei stain quite well; occasional red blood cells in tubules; no casts, but occasional desquamated epithelial cells.

Spleen: Shows quite large nodules, rather increased vascularity. The splenic sinuses are large, dilated, empty. The pulp shows many red blood cells.

Mesenteric Lymph Nodes: Large, the one sectioned measuring about 1 cm. in diameter, with a very large artery and vein in the center. Most of the section shows lymphoid tissue with some increase of connective tissue and congested vessels. One large area, macroscopically visible, is necrotic, has numerous polymorphonuclear cells with small necrotic nuclei, and pink staining fibrous debris.

Liver: Shows quite large sinuses with numerous red blood cells. About the central veins, the hepatic cells appear smaller, but stain well.

We did not have all the mediums necessary for the proper isolation of typhoid bacilli, so we sent a subculture of the spinal fluid taken the day before death to Dr. Noble Sherwood, whose report was, in part, as follows:

"The culture as received contained two organisms, a gram-negative rod and a gram-positive spore producer. I plated them immediately, and beg to report the gram-negative rod as a slightly atypical strain of *B. typhosus*. Its reaction to the gram stain is typical, but the motility is so slight as to be negligible. I have repeatedly observed that freshly isolated strains of *B. typhosus* were frequently either nonmotile, or slightly motile for several generations after isolation, and then they would suddenly become actively motile. This is more especially true when organisms have been isolated from the blood stream, rather than from feces.

"The strain sent in by you does not produce any acid or gas in saccharose; this is typical. It gives acid, no gas in dextrose and mannite, these reactions are typical. It seems to show a tendency to acidify lactose; this is an atypical reaction. However, this strain is identical in its action on lactose as in a European strain of *B. typhosus* we have under observation. The reaction in gelatin shows no liquefaction, which is typical for *B. typhosus*.

"Now, the agglutination test with a polyvalent antityphoid serum shows agglutination in dilution of 1:3,000. The other laboratory strains, such as the New York Board of Health and the Bender strain, show agglutination in 1:8,000 and 1:10,000 dilutions. We have isolated quite a number of strains, however, that show agglutination in dilutions higher than your strain and less than the other strains.

"I feel no doubt that the organism you are working with is *B. typhosus* and apparently quite similar to the European strain which we have been working with."

To verify these findings, we also sent a subculture to Dr. F. J. Hodges, Department of Pathology, Washington University Medical School, St. Louis, and append part of his report. (Unfortunately, both specimens sent seem to have been contaminated, as in our earlier cultures we found only one gram-negative short bacillus. Our later cultures here were contaminated by a gram-positive, large, thick bacillus.)

"There are three organisms in the original cultures. One a gram-positive spore former overlooked in the first smears because of the great preponderance of gram-negative bacilli of two morphologic types. One gram-negative bacillus is very short and fat. The other, recovered from isolated colony on agar plate, is nearly twice as long, and little, if any, wider. The gram-positive organism was discarded. Both gram-negative strains gave typical sugar results for typhoid (when mixed with the gram-positive spore former, the sugar reactions were atypical) and both gram-negative strains are agglutinated by the stock typhoid serum. In cross agglutination tests, Para 'A' and Para 'B' and the dysenteries, the results are widely different for the two organisms, indicating that both morphologically and serologically we have here two types of typhoid bacillus.

"These two types labeled and sent to us as B I and B II, agglutinated the stock typhoid serum at 1:6,000 and 1:24,000, respectively. B II was agglutinated by various low dilutions of both Para A and B serum, and by Flexner's serum, but neither by Shiga bacillus serum in any concentration."

We had begun a thorough collection of the reported cases of typhoid meningitis, intending only to summarize the purulent cases since Cole's paper.[1] Then we found Bayne-Jones'[2] article, published in 1917, although apparently prepared in 1915. We have found only a few cases that he has not noted, and have completed the table for comparison with Cole cases.

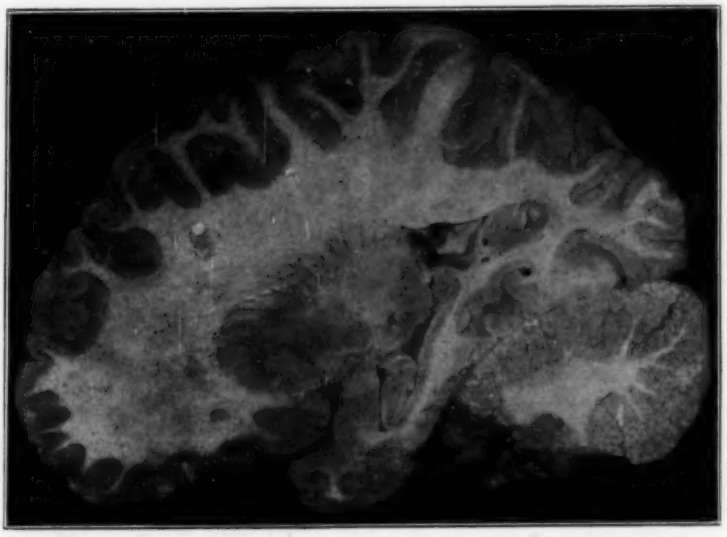

Fig. 2.—Photograph of a cross section of the left half of the brain.

McCrae[3] cites a case of typhoid fever, diphtheria and acute encephalitis. The diphtheria bacillus was found early in the disease, but disappeared after a few days; the blood culture gave a pure typhoid growth and the Widal was positive. The necropsy report showed a reddish sphenotemporal lobe, and thrombosed vessel in this part, but, unfortunately, no cultures were made from the brain.

Schwartz reviewed some of the cases reported by Cole, and thinks that contamination of the spinal fluid may take place through the blood which is known to contain the *B. typhosus*. He would exclude these

1. Cole, R.: Typhoid Meningitis, Johns Hopkins Hosp. Rept. **12**:299, 1904.
2. Bayne-Jones, S.: Typhoid Meningitis, Report of a Case, Am. J. M. Sc. **154**:55, 1917.
3. McCrae, J.: Two Unusual Occurrences in Typhoid Fever, Acute Encephalitis and Perforation of the Sigmoid Flexure, Lancet **1**:712, 1905.

Summary of Cases of Purulent Typhoid Meningitis

Author	Sex	Age	Diagnosis	Meningeal Symptoms	Onset of Meningeal Symptoms, Day	Day of Death	Laboratory Findings	Necropsy	Bacteriologic Data
Crouchet et Buard, 1902	M	13	Typhoid	.....	35th	37th	35th day, spinal fluid turbid; culture, pure typhoid	None	
McCrae, 1905	M	22	Typhoid	Drowsy, delirious....	8th	14th	13th day, Widal positive; blood culture, pure typhoid	Temporal lobe, thrombosed; vessel, small cell infiltration and perivascular	Incomplete
Delille, 1905	F	9	Typhoid	.....	21st	28th	Spinal fluid turbid; culture, pure typhoid; postmortem same	Purulent meningitis, usual typhoid lesions	
Stäubli, 1905	M	22	Typhoid	Headache..... Stiff neck; Kernig....	3d 17th	22d	7th day, spinal fluid negative; 10th day, Widal 1:100; 21st day, spinal fluid cloudy, polymorphonuclears, agglutinated typhoid bacilli 1:100; culture, pure typhoid, agglutinated by typhoid serum	Purulent meningitis, few typical typhoid lesions	Good
Henry and Rosenberger, 1908	M	34	.....	Delirium.....	3d	9th	7th day, spinal fluid negative; 9th day, same, polymorphonuclears, typhoid-like bacilli agglutinated by known serums 1:40; blood culture same; postmortem spinal fluid same	Purulent meningitis, no intestinal lesions	Good
Southard and Richards, 1908	M	31	Taboparesis	Unconscious.....	5th	7th	Postmortem spinal fluid culture, pure typhoid, agglutinated by typhoid serums 1:5,000	Polymorphonuclear infiltration of pia mater; no intestinal lesions	Good
Lavenson, 1908	F	26	Typhoid	.....	....	....	Spinal fluid turbid; culture, pure typhoid	Purulent meningitis, no intestinal lesions	Good
Symmers and Wilson, 1909 Milligan, 1909	M	37	.....	Delirious.....	10th	14th	14th day, Widal positive; postmortem spinal fluid, purulent; culture, pure typhoid	None	
Schwartz, 1910	M	8	Typhoid	Stupor.....	14th	19th	15th day, Widal negative; 19th day, spinal fluid turbid; lymphocytes; culture, pure typhoid, agglutinated by typhoid serums 1:100	None.....	Good. Spinal fluid obtained before death
Lemierre et Joltrain, 1912	M	47	Otitis meningitis	Vertigo..... Delirious.....	2d 4th	7th	3d day spinal fluid turbid; polymorphonuclears 90%; culture, pure typhoid, agglutinated by typhoid serums 1:10; spinal fluid agglutinates typhoid bacilli 1:20	Purulent meningitis, usual typhoid lesions	Good
Lyall, 1912	F	4 mo.	.....	Opisthotonus..... Improved..... Unconscious.....	1st 6th 34th	36th	6th day, spinal fluid clear; 9th day, spinal fluid culture negative; 17th and 19th days, same; 34th day, cloudy; polymorphonuclears; culture, atypical typhoid, agglutinated by known typhoid bacilli, after many generations	Purulent meningitis, large mesenteric glands	Good
Lesieur et Marchand, 1912	M	41	Typhoid	.....	28th	29th	Spinal fluid turbid; culture, pure typhoid; blood culture same	Purulent meningitis, no intestinal lesions	Good

O'Carroll and Purser, 1912	M	9	.....	Rigor.....	17th	22d	5th day, Widal positive; 8th day, spinal fluid negative; 21st day, spinal fluid turbid; 1,100 cells; 60% polymorphonuclears; culture, pure typhoid, agglutinated by typhoid serums 1:50	Purulent meningitis, no spleen or intestinal lesions	Good
Planche et Lombard, 1914	M	2	Typhoid	.....	24th	27th	Spinal fluid purulent; culture, pure typhoid	Purulent meningitis, no intestinal lesions	Fair
	M	8	Typhoid	.....	35th	36th	Spinal fluid culture, pure typhoid; postmortem culture of lungs, pneumococcus	Purulent meningitis, usual typhoid lesions	
d'Oelsnitz et al., 1915	M	23	Infraorbital wound	Rigor.....	18th	24th	10th day, Widal 1:10; 20th day, spinal fluid cloudy; increase in cells; culture, pure typhoid, agglutinated by typhoid serums 1:100; 21st day, Widal positive	None.....	Good
Ortoconni et Amenille, 1915	M	28	.....	Stupor..... Coma.....	5th 8th	8th	5th day, blood culture, pure typhoid; 8th day, spinal fluid clear; increase in cells; culture, pure typhoid, agglutinated by typhoid serums	Congestion of brain, increase of fluid; usual intestinal lesions	Good
Robinson, 1915	M	55	Meningitis	Coma.....	1st	4th	2d day, spinal fluid turbid; increase cells; culture, pure typhoid; 3d day, same, agglutinated by typhoid serums 1:50, serum from this agglutinated known typhoid 1:2,000	None.....	Good
Bayne-Jones, 1915	F	19	Typhoid	Violent headaches... Improved..... Kernig positive.....	10th 11th 19th	28th	21st day, spinal fluid negative; 22d day, blood culture, pure typhoid; 24th day, spinal fluid turbid; increas in cells; culture, pure typhoid, agglutinated by typhoid serum 1:3,200	Purulent meningitis, usual typhoid lesions	Good
Bonnamour et Macrygenis, 1917	F	25	Typhoid	Stupor..... Convulsion.....	14th 24th	28th	6th day, Widal negative; 10th day, spinal fluid negative; 15th day, Widal 1:50; blood culture, pure typhoid, agglutinated by typhoid serums; 23d day, spinal fluid, increase in cells; 60% lymphocytes; 26th day, spinal fluid turbid, no agglutination with typhoid bacilli; 28th day, spinal fluid purulent; 88% polymorphonuclears; culture, pure typhoid, agglutinated by typhoid serum 1:250, agglutinated typhoid bacilli 1:1,000	Purulent meningitis, more anteriorly; spleen negative; usual typhoid lesions	Good
Merklen et Gautier, 1917	M	32	Typhoid	Comatose, Kernig, involuntaries	?	?	Spinal fluid, many polmorphonuclears; culture, pure typhoid, agglutination positive	Purulent meningitis.....	Good
Cintra, 1918	M	33	.....	Comatose.....	3d	4th?	4th day, Widal negative; blood culture, pure typhoid; spinal fluid, increase polymorphonuclears; culture, pure typhoid, agglutinated by typhoid serums 1:100 and 1:8,000; positive Wassermann	Purulent meningitis.....	Good
Authors'	M	6	Typhoid	Rigid, involuntaries. Improved..... Otitis, involuntaries	7th 11th 21st	23d	22d day, spinal fluid turbid; increase in cells, lymphocytes; culture, pure typhoid; postmortem same; two strains of typhoid: B1 agglutinated 1:6,000, B2 agglutinated 1:24,000	Purulent meningitis, more anteriorly; typhoid spleen; slight intestinal lesions	Good

cases where such contamination during spinal puncture may have occurred.

Lyall [4] regarded Neuman and Schaffer's [5] case as being one of true purulent typhoid meningitis. Of course, the now known laboratory tests were not applied, but it appears that their tests were conclusive, since only the potato culture was questionable. In Lyall's own case, the culture showed an atypical typhoid, in that only after several generations was it motile, and then only slightly. Then, only, was it agglutinated by known typhoid serums, but best by an homologous serum which agglutinated also known typhoid bacteria.

O'Carroll and Purser [6] noted Osler's eleven cases of central nervous system lesions in two thousand cases of typhoid, and Curschman's five in his own experience, but, unfortunately, bacteriologic examinations were not complete. O'Carroll found fifteen reported cases where typhoid bacilli alone caused a meningitis, and estimated that there are not more than thirty cases in all. They believed that the purulent condition of the brain is only an advanced stage of an edema often described—with which we, of course, agree.

D'Oelsnitz [7] and Amenille [8] described cases with increased cell count in the spinal fluid, but no turbidity nor increased pressure, and the latter briefly described another case which cleared up for them after the postmortem examination.

An astonishing finding to us, and one already noted by others (Fernet [9]) is the frequent lack of the usual typhoid lesions, although many of the cases showed positive Widal and blood cultures. In six cases here recorded, special mention was made that little or no intestinal lesions were present; in some, the spleen was quite normal. In our case, there was no evidence of intestinal lesion, except one inch above the ileocecal valve. The mesenteric glands and spleen were markedly enlarged. In our case, too, the marked dilatation of ureters and urinary tubules with no apparent cause was noted. Of course, we must admit that the intestinal lesions may have healed. Against this theory in many cases, is the relatively short course of the disease.

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4. Lyall, H. W.: Meningitis in an Infant Caused by the Typhoid Bacillus, J. Med. Res. **22**:457, 1912.

5. Neuman, H., and Schaeffer, R.: Zur Aetiologie der eitrigen Meningitis, Virch. Arch. **109**:477, 1887.

6. O'Carroll, J., and Purser, F. C.: On a Case of Meningitis Due to Bacillus Typhosus, Tr. Roy. Soc. Med. Ireland **30**:108, 1912.

7. d'Oelsnitz, M., Bourcart, G., and Ronchese, M. A.: Un cas de méningite cérébro spinale éberthienne, Bull. et mém Soc. méd. d. hôp. de Par. **39**:276, 1915.

8. Ortoconni, A., and Amenille, P.: Accidents méninges précoces dans la fièvre typhoide, Bull. et mém. Soc. méd d. hôp. de Par. **31**: 187.

9. Fernet, Ch.: Méningite typhoïde par bacille d'Eberth, Bull. et mém. Soc. méd. d. hôp. de Par., 1891, p. 361.

In several cases were noted—and this is particularly true in Bonnamour and Macrygenis [10] and our cases — that the anterior portion of the brain showed a more marked purulent condition than the posterior. This is evident even in the photograph, but was especially noted at the postmortem table. However, a collection of pus below the cere-

Fig. 3.—Photograph of a 10 micron section of the meninges over the frontal lobe (ocular, 4; objective, 3 [Leitz]).

bellum was also noted. The ventricles in our case, differing from others, were not enlarged, but contained a turbid fluid on examination.

10. Bonnamour, S., and Macrygenis, A.: Méningite aiguë purulente eberthienne au cours d'un fièvre typhoïde. Presence du bacille d'Eberth dans le liquide céphalo-rachidien, Lyon méd. **126**:397, 1917.

Lesieur and Marchand [11] were able to find only nine cases in the literature in which the typhoid bacillus had been grown from the spinal fluid before death. Fifteen of the cases reported herein specifically state that the typhoid organism was isolated during life from the spinal fluid. Cole's [1] table does not state whether culture was made before or after death. In some, apparently, they were made at the postmortem; in one, on the day of death; in others, the time is not quite clear. However, we have reviewed other cases, not here tabulated, in which the typhoid bacillus was obtained from the spinal fluid where no purulent condition supervened, and where death did not follow. These probably belong to Cole's serous meningitis cases. Cole, in thirteen cases of serous meningitis, shows that in six the typhoid bacillus was grown from the spinal fluid in pure culture during life, and that it was grown from the others after death. Therefore, quite occasionally, the typhoid bacilli may be grown, although there is no change in the gross appearance of the spinal fluid.

In only six cases did Lemierre and Joltrain [12] find a primary typhoid meningitis — or rather, one apparently not following intestinal typhoid — as their case showed an otitis media very early, although, as they stated, the meningitis may not have been secondary to the otitis. Apparently, two other cases in our table were either primary or secondary to a typhoid other than intestinal — one of them to an infraorbital war wound. In several of the cases occurring in soldiers, no clear history was obtainable. These may have had a primary abdominal infection.

Lemierre and Joltrain also point out the peculiarity in meningitis cases of the spinal fluid agglutinating the organism. They believe that this is exceptional, as it has been stated that agglutinins, although present in blood, have not been observed in the spinal fluid. In their case, the spinal fluid agglutinated the organism grown from it, and also laboratory strains. Bayne-Jones [2] states that in serous cases, the spinal fluid contains agglutinins for *B. typhosus*.

Several investigators found a clear fluid in early lumbar punctures, and later, turbidity and increased pressure. In only very few was a definite cell count reported. O'Carroll and Purser [6] and Lemierre and Joltrain [12] reported relatively high polymorphonuclear leukocytes in their earlier counts, although in the latter, a later count showed an increase of small round cells. Bonnamour and Macrygenis [10] reported

11. Lesieur, C., and Marchand, M. J.: Etat méningé au cours d'un fièvre typhoïde. Evolution bénigne apres la ponction lombaire, Bull. et mém. Soc. méd. d. hôp. de Par. **34**:785, 1912; Ibid., 780.

12. Lemierre, A., and Joltrain, E.: Méningite purulente Eberthienne début par symptomes d'otite aiguë, Bull. et mém. Soc. méd. d. hôp de Par. **34**: 581, 1912.

in their first count a predominance of lymphocytes and in a later count 80 per cent. polymorphonuclears. Unfortunately, no differential count was made in either of our counts, but there was noted a predominance of mononuclears.

MacCallum [13] carefully described the minute pathology of typhoid meningitis. Others [14] have found in general the same results as MacCallum. Our sections do not show the congestion of the veins, nor the blocking of the arteries by a cellular infiltration of the vessel wall and an endarteritis, as MacCallum appears to have found. In fact, we see in our sections that the cellular infiltration is less marked about the blood vessels than elsewhere, especially about the veins. It is possible that we are dealing with a more recent meningeal involvement than MacCallum had, for Cole noted that in that case meningeal symptoms were marked for one week before death with the bacilli already in the spinal fluid.

In our table, which includes twenty-three cases, the ages of the patients vary from 4 months to 55 years. There are eighteen males and five females. Cole's patients varied in age from 4 to 46 years, with five males and three females, three under 20 years, two over 40. Our table shows nine patients under 20 and three over 40 years of age.

Symptoms of meningeal irritation are so frequent in typhoid cases that it is difficult to judge when the real meningitis begins. If daily spinal punctures are made, of course, the date of a turbid fluid might be an index. So far, we know of no definite symptom that can be taken as an index of a purulent meningitis. In our case, were an early restlessness, involuntary voiding of urine and feces, and rigidity an index of purulent meningitis? Of meningeal irritation, of course! Or was this the second stage, after the gallbladder involvement, with otitis, involuntary voiding of urine and feces and convulsions? We have taken the latter view. And so, in other cases, we have taken what seemed to be the final meningeal flare-up before death as the stage of onset of purulent meningitis. Judging thus, we find its onset varies

13. MacCallum, W. G.: The Pathological Anatomy of Meningitis Due to Bacillus Typhosus, Johns Hopkins Hosp. Rept. **12**:411, 1904.

14. Cintra, U.: Meningite purulenta com bacillo de Eberth isolado do liquido cephalo-rachiano, Ann. Paulistas de méd. e Cir. **9**:64, 1918. Crouchet and Buard: Sur un cas de méningite cérébro-spinale typhique, aver présence du bacille d'éberth dans le liquide céphalo-rachidien, Gaz. hebd. d. sc. méd. de Bordeaux, 1902. Delille: Pediat. prat. Lille **3**:89, 1905. Lavenson, R. S.: Univ. Penn. Med. Bull. **21**:55, 1902. Merklen and Gautier: Méningite aiguë éberthienne à forme purulente. Présence du bacille typhique dans le liquid céphalo-rachidien, Presse méd., Jan. 22, 1917, p. 51. Milligan, E. H. M.: Isolation of the Typhoid Bacillus from the Spinal Fluid from a Case of Typhoid with Cerebrospinal Symptoms, Brit. M. J. **1**:1295, 1908. Nietter, A.: Ueber den Nachweis vom Typhusbazillen der Zerebrospinalflüssigkeit bei typhus Abdominalis, München. med. Wchnschr. **55**:1009, 1908.

from the first to the thirty-fifth day. Symptoms lasted then, for from one to ten days, some showing convulsions, but many with other meningeal symptoms of involuntary sphincteric relaxation, vomiting, intense headache, contraction of various muscles, frequently of the hands and face. Cole found that symptoms began late, from the second to the fifth week, and lasted for from two to five days.

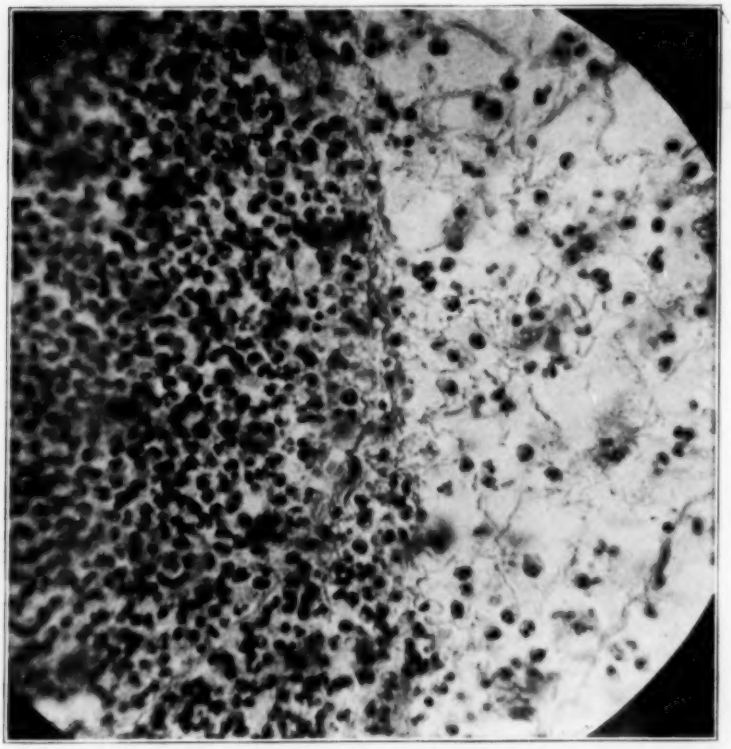

Fig. 4.—Photograph of the meninges near a blood vessel showing perivascular infiltration and the denser infiltration away from the blood vessels (ocular, 4; objective, 6).

We have not accepted two of the cases put in Bayne-Jones report, one by Gurd and Nelles [15] which seems to have been an abscess above the dura, following an injury, and not a meningitis, even though

15. Gurd, F. B., and Nelles, T. B.: Intracranial Abscess Due to the Typhoid Bacillus, Ann. Surg. **47**:4, 1908. Henry, J. N., and Rosenberger, I. C. R.: Purulent Cerebrospinal Meningitis Caused by the Typhoid Bacillus without the Usual Intestinal Lesions of Typhoid Fever, Am. J. M. Sc. **135**:240, 1908.

typhoid bacilli were isolated. The other (Raymond and Siccard [16]) was an infection localized in the lumbar region, from which pus and a pure culture of typhoid was obtained. After laminectomy, the patient recovered. To us, it seems that purely localized typhoid infection of the meninges, especially with recovery, should not be included.

The prognosis, as shown by our table, is very bad. Excepting the two cases, quoted above, neither of which is included in our table, there have been no recoveries. It is to be remembered, that in thirteen cases of serous meningitis Cole found only one recovery. Although Bayne-Jones does not give the number of recoveries from serous meningitis in his table, he quoted Claret and Lyon-Caen as having found eight recoveries in thirteen cases. Cole showed that there were no recoveries in his fourteen cases of purulent meningitis.

The question of treatment may seem out of place in a disease which has been so uniformly fatal. Possibly prophylaxis offers the best hope. Lemierre and Joltrain,[12] after removal of spinal fluid, introduced electrargol, evidently with no results. But since some recoveries occur in some serous cases, and some have noted a marked improvement following lumbar puncture, repeated punctures may help. Even in some cases with amelioration of symptoms after puncture, which usually showed clear fluid, a purulent fluid formed later and death supervened.

To us, it seems that a purulent spinal fluid, with cultures showing typhoid bacilli, is proof enough of a typhoid meningitis. Of course, this does not mean that necropsies should not be obtained; nor that other organisms may not be responsible. But even in mixed infections, except for statistical reports, what does it matter if other organisms are present?

Purulent typhoid meningitis has been noted usually following abdominal typhoid, but also as secondary to other typhoid as witness one otitic and one infraorbital wound.

Cole reported fourteen cases and Bayne-Jones eighteen. We have ruled out two of the latter and added seven more. All gave pure typhoid cultures from the spinal fluid, most of them before death. In all these cases the organism has been isolated with a fair degree of accuracy. All cases noted have terminated fatally.

16. Raymond, F., and Siccard, J. A.: Epidurite purulente lombaire a bacilles d'Eberth dans la convalescence d'une fièvre typhoide. Paraplégie. Ponction lombaire, Bull. et mém. Soc. méd. d. hôp. de Par. **22**:860, 1905. Robinson, J. E.: Case of Primary Typhoid Meningitis, South. M. J. **8**:37, 1915. Southard, E. E., and Richards, E. T. F.: Typhoid Meningitis, J. Med. Res. **19**:513, 1908. Staubli, C.: Meningismus typhosus und Meningotyphus, Deutsch. Arch. f. klin. Med. **82**:90, 1905. Symmers and Wilson: J. Path. & Bacteriol. **13**:251, 1909 (quoted from Bayne-Jones). Stühmer, A.: Typhusbazillen in der Zerebrospinalflüsigkeit, München. med. Wchnschr., 1911, p. 357.

OBSERVATIONS ON CHANGES IN FORM OF THE INITIAL VENTRICULAR COMPLEX IN ISOLATED DERIVATIONS OF THE HUMAN ELECTROCARDIOGRAM

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The literature of recent years has contained numerous contributions dealing with abnormalities of the initial ventricular complex Q R S of the electrocardiogram. Most authors,[1] however, have dealt largely with changes affecting all derivations consisting of abnormalities in complex contour or increase in the complex base width exceeding the recognized normal.[2]

Differences of opinion exist as to the cardiac disorder responsible for these deviations from the normal. Most observers, I believe, recognize myocardial changes affecting the ventricular conduction system, locally or diffusely. Robinson [3] takes issue with the majority, and emphasizes the rôle of functional myocardial fatigue. He presents electrocardiograms of a patient in which the aberrant complexes approach normal, yet do not attain normal after digitalis and rest. I have not had the opportunity of observing the abnormal complexes return to normal when all three derivations have been affected. In a previous article [4] I called attention to the high mortality attending this disorder, and emphasized the progression of the disease. The obvious criticism of this article is the paucity of necropsy material and the incomplete histologic data. Careful serial histologic examinations have been in progress for some time and will be reported later.

The fact that these patients rapidly show myocardial disintegration and die seems to me to indicate structural changes, in the majority of instances at least, even in the absence of conclusive pathologic data.

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1. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med. **22**:331 (Sept.) 1918.

Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916.

2. Lewis, T.: Clinical Electrocardiography, London, Shaw, 1913, p. 120.

3. Robinson, G. C.: The Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med. **24**:422 (Oct.) 1919.

4. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

The frequency of abnormalities of the Q R S complex in isolated derivations of the electrocardiograms prompted this study to determine, if possible, the clinical significance of these findings. Wedd[5] published thirty such cases, in twenty-one of which a definite clinical diagnosis of heart disease was made, and in nineteen of which myocardial disease was noted. Three cases were diagnosed syphilis and one case was diagnosed chronic nephritis without reference to the cardiovascular system. In five cases no clinical diagnoses were

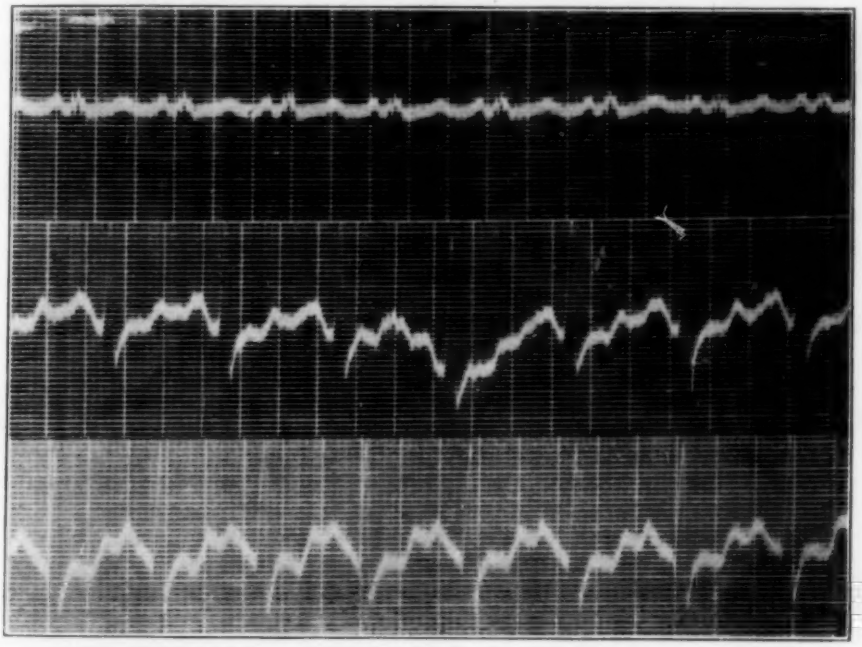

Fig. 1 (Case 172,578).—Notched Q R S, Derivation 1.

recorded. In conclusion, Wedd states "Slight notching or localized thickening of the R complex of the electrocardiogram is frequently encountered in cases of unquestioned myocarditis . . . While no quantitative value can be assigned to such notching, it is believed, when permanent, to indicate pathologic changes in the myocardium, and when transient to reveal a temporary or potential defect in the conduction system . . ."

5. Wedd, A. M.: The Clinical Significance of Slight Notching of the R-wave of the Electrocardiogram, Arch. Int. Med. **23**:515 (April) 1919.

This study comprises 747 cases and covers a period of five and one-half years. The cases were divided into two major groups, cases (550) with Q R S complexes definitely notched, and cases (197) with slurring or localized thickening of the ascending or descending limb, or both. Both groups were subdivided according to derivation occurrence. The accompanying electrocardiograms illustrate the abnormalities under discussion (Figs. 1-6).

Notched Q R S Complexes.—Seventy-seven cases (14 per cent.) were placed in Derivation 1, eighty-three (15.1 per cent.) in Derivation 2, and the greatest number, 390 (70.9 per cent.) in Derivation 3. In more than one half (53.1 per cent.) of the cases, the electrocardiograms were associated with preponderance of the left ventricle. Table 1 illustrates this occurrence. This relationship at once directs attention to the left ventricle as the possible seat of disturbance at least in the majority of cases.

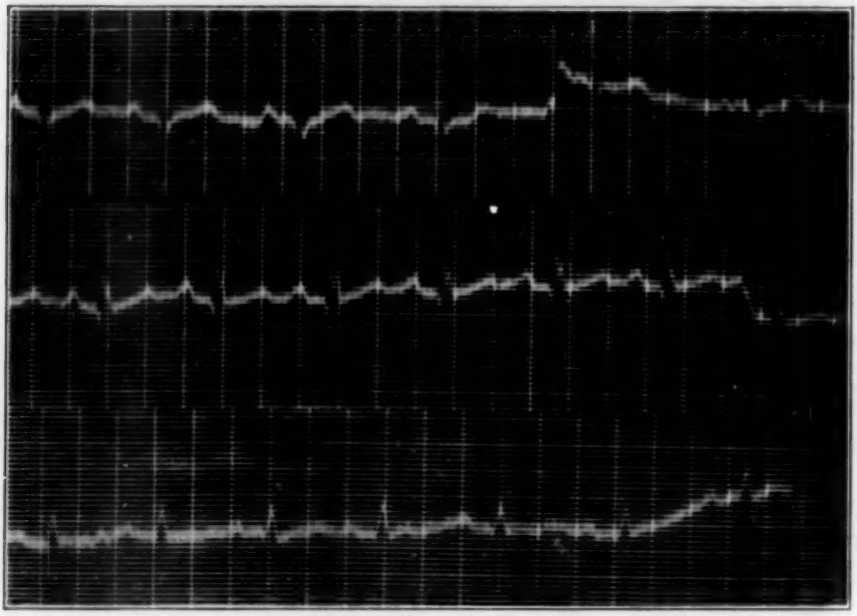

Fig. 2 (Case 293,424).—Notched Q R S, Derivation 2.

Etiologic disorders occurring in this group in order of frequency were (1) degenerative processes, (2) infections, (3) local nutritional disturbances, and (4) congenital heart disease. These findings are summarized in Table 2.

There was definite evidence of heart disease in all except eighty-one cases (14.7 per cent.). This group was clearly separated in order to avoid confusion in the final analysis, but it is recorded because the electrocardiographic findings were clear cut. The elapse of more time may throw light on this extremely interesting group.

Negativity of the final ventricular T wave occurred in almost half the cases (41.8 per cent.), and was most frequently observed in Derivation 3 (66.4 per cent.). There was no instance of T wave negativity in Derivation 2, or in Derivations 1 and 3 in combination. This summary is found in Table 3.

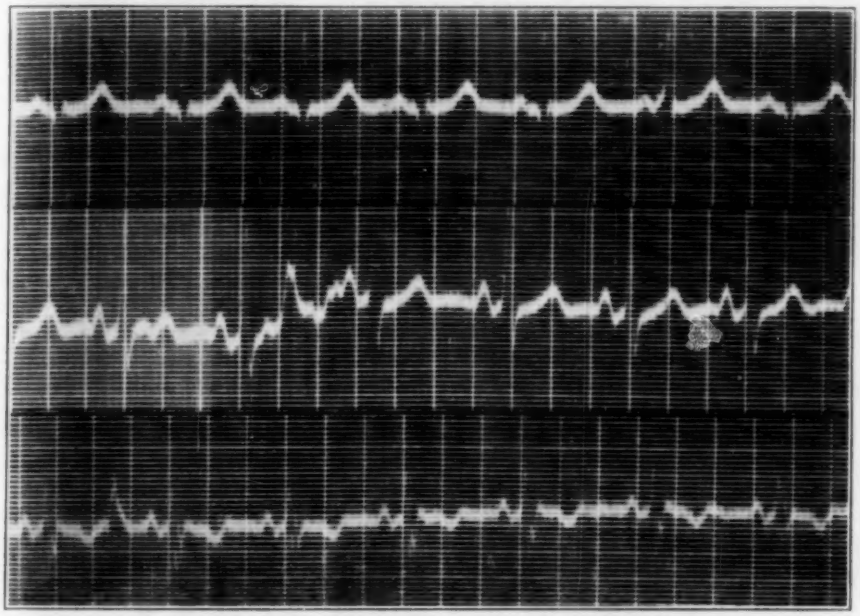

Fig. 3 (Case 297,104).—Notched Q R S, Derivation 3.

Auricular fibrillation occurred in seventy-six cases (13.8 per cent.); this infrequency seems to indicate that these patients as a group are still possessed with relatively efficient myocardiums. Delay in auriculoventricular conduction occurred in only six cases.

Information has been received concerning 410 patients; ninety-seven (23.7 per cent.) of these have died from heart disease. The highest mortality occurred in Derivation 2 (37 per cent.). A control series corresponding in number, sex and occurrence by decade, and excluding the graver types of heart disease, such as angina pectoris, aneurysm, arborization block, disease of the auriculoventricular bundle

TABLE 1.—Ventricular Preponderance in Notched Complexes

Decade	Derivation 1			Derivation 2			Derivation 3		
	Left Preponderance	Right Preponderance	No Preponderance	Left Preponderance	Right Preponderance	No Preponderance	Left Preponderance	Right Preponderance	No Preponderance
1-10	3	0	1	0	1	0	2	0	2
11-20	4	0	4	1	0	0	8	3	8
21-30	6	7	10	3	3	0	28	9	25
31-40	4	1	7	4	4	2	35	10	37
41-50	4	4	3	14	3	1	52	10	37
51-60	5	2	6	23	1	2	47	6	23
61-70	2	0	3	14	1	4	25	1	15
71-80	1	0	0	2	0	0	5	0	2
	29	14	34	61	13	9	202	39	149

TABLE 2.—Etiologic Conditions in Notched Complexes

	Total	Degenerative Processes			Infections			Nutritional Disturbances			
		Hypertension With and Without Chronic Nephritis	Exophthalmic Goiter	Adenomas With Hyperthyroidism	Endocardial Valvular Disease	Chronic Myocarditis	Syphilis	Arteriosclerosis	Angina Pectoris Patient with Arteriosclerosis	Congenital Heart Disease	Inconclusive Clinical Cardiac Findings
Derivation 1	77	6	11	4	39	6	5	3	1	0	3
Derivation 2	83	24	2	3	17	14	3	9	8	3	8
Derivation 3	390	69	84	26	63	42	14	21	12	1	70
Total	550	99	97	33	119	62	22	33	21	4	81
Percentage		18.0	17.6	6.0	21.6	11.3	4.0	6.0		0.07	14.7
		41.6			36.9						

TABLE 3.—T Wave Negativity in Notched Complexes

Notched QRS	Total Notched QRS	T Derivation 1	T Derivation 2	T Derivation 3	T Derivations 1 and 2	T Derivations 2 and 3	T Derivations 1 and 3	T Derivations 1, 2 and 3
Derivation 1	77	1	0	20	1	7	0	2
Derivation 2	83	12	0	18	6	6	0	3
Derivation 3	390	21	0	116	4	12	0	3
Total	550	34	0	154	11	25	0	8
Percentage		14.7	0.0	66.4	4.7	10.8	0.0	3.4
		232 (41.8%)						

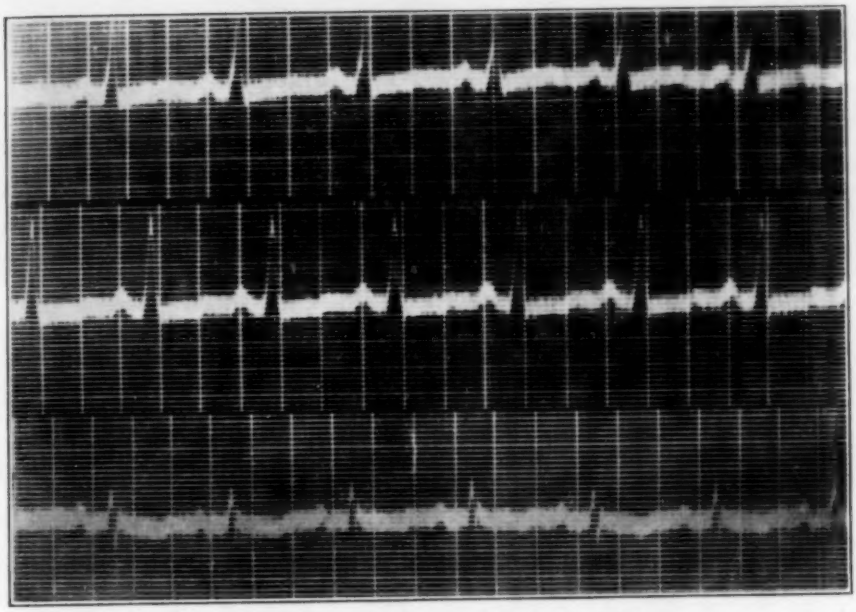

Fig. 4 (Case 287,083).—Slurred Q R S, Derivation 1.

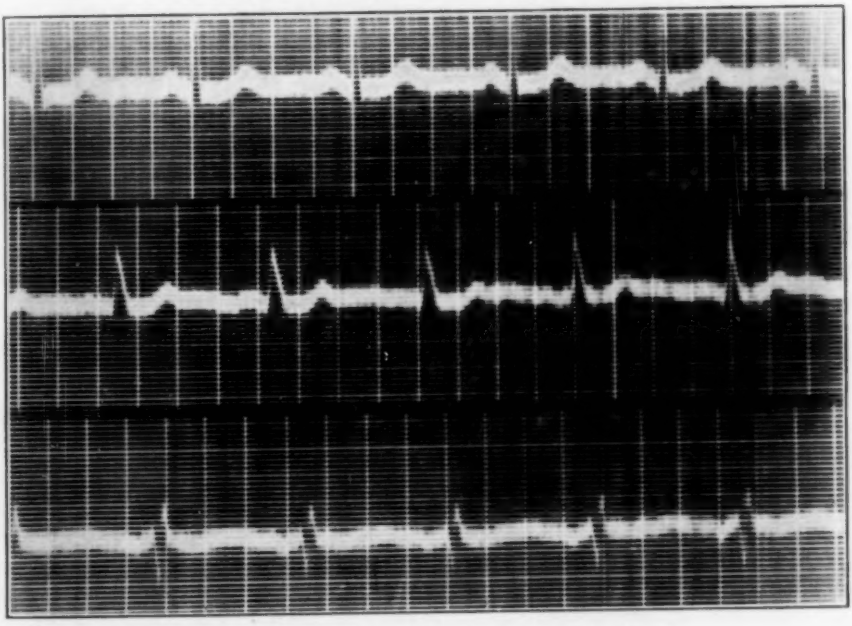

Fig. 5 (Case 271,992).—Slurred Q R S, Derivation 2.

TABLE 4.—MORTALITY IN NOTCHED COMPLEXES, DERIVATION 1

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1-10	4	3	1	2	1	.....	2	0	2	0	0
11-20	5	4	0	4	2	.....	1	1	0	0	0
21-30	23	11	5	6	0	.....	11	4	5	2	0
31-40	12	9	3	6	4 x	*x Pneumonia	5	4	1	0	1
					y	y Influenza					
					z	z Abdominal hemorrhage					
41-50	11	8	2	6	4	.....	4	2	0	2	0
51-60	13	10	4	6	4	.....	6	2	3	1	0
61-70	5	4	3	1	2 x	x Cancer of the rectum	2	2	0	0	0
71-80	1	1	1	0	0	.....	1	1	0	0	0
Total	77	50	19	31	18	.....	32	16	11	5	1

14 cardiac deaths, 28 per cent.

* Each letter refers to a single death other than cardiac.

TABLE 5.—MORTALITY IN NOTCHED COMPLEXES, DERIVATION 2

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1-10	1	1	1	0	0	.....	1	0	0	1	0
11-20	1	0	0	0	0	.....	0	0	0	0	0
21-30	6	3	1	2	1	.....	2	0	0	2	0
31-40	10	6	1	5	2 x	x Pneumonia	4	1	2	1	0
41-50	16	11	6	5	3	.....	8	3	5	0	0
51-60	26	18	12	6	8	.....	10	2	6	2	0
61-70	19	13	11	2	5	.....	8	2	3	3	0
71-80	2	2	2	0	2	.....	0	0	0	0	0
Total	85	54	34	20	21	.....	33	8	16	9	2

20 cardiac deaths, 37 per cent.

TABLE 6.—MORTALITY IN NOTCHED COMPLEXES, DERIVATION 3

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1-10	4	2	1	1	0	.....	2	0	1	1	1
11-20	19	14	4	10	3	.....	11	1	8	2	2
21-30	62	50	19	31	8	.....	42	10	23	9	7
31-40	82	61	24	37	8 x	x Diabetes	53	19	24	10	10
					y	y Influenza					
41-50	90	80	29	51	18 x	x Nephritis	62	23	22	17	10
					y	y ?					
51-60	76	59	37	22	21 w	w Cancer	38	9	18	11	1
					x	x ?					
					y	y Cancer of the pancreas					
					z	z Pneumonia					
61-70	41	36	25	11	15 x	x Pneumonia	22	8	7	8	2
					y	y Tuberculosis					
					z	z ?					
71-80	7	4	4	0	3	.....	1	0	1	0	0
Total	380	306	143	163	74	.....	232	70	104	58	30

63 cardiac deaths, 20.6 per cent.

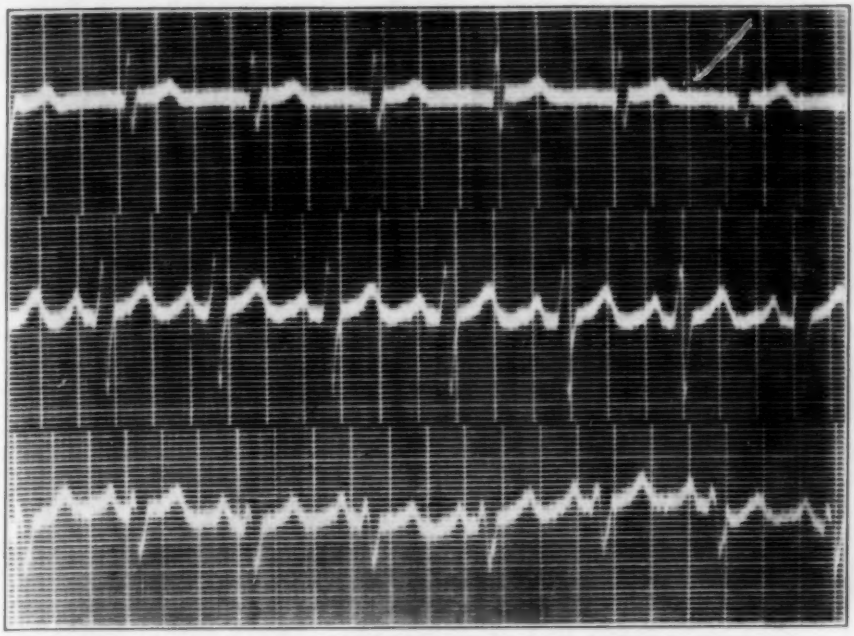

Fig. 6 (Case 233,897).—Slurred Q R S, Derivation 3.

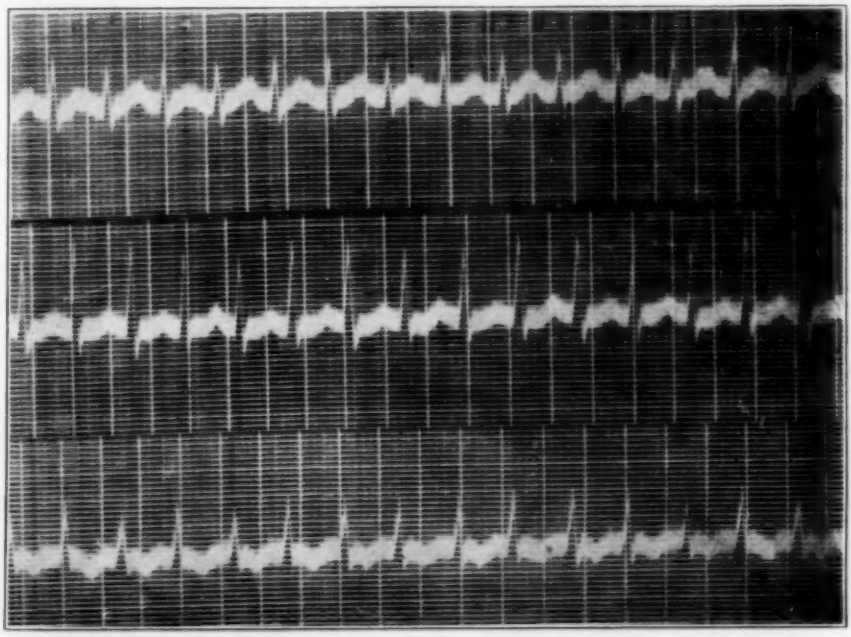

Fig. 7 (Case 252,579).—Slurred Q R S, Derivation 3. Negative T wave, Derivation 3. Nodal tachycardia. Feb. 28, 1919.

TABLE 7.—Total Mortality in Notched Complexes

	Total	Patients Heard From	Males	Females	Cardiac Deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac Symptoms
Derivation 1	77	50	19	31	14	28.0	32	16	11	5	1
Derivation 2	83	54	34	20	20	37.0	33	8	16	9	12
Derivation 3	209	306	143	163	63	20.6	232	70	104	58	36
Total	550	410	196	214	97	23.7	297	94	131	72	39

TABLE 8.—Control Series

Decade	Total	Patients Heard From	Males	Females	Deaths			Deaths Other than Cardiac	Living	Worse	Improved	Unchanged
1-10	9	6	3	3	1				5	2	1	2
11-20	28	17	7	10	3	x	x	Thyroidectomy (exophthalmos)	14	4	6	4
						y	y	Hyperthyroidism				
21-30	91	63	23	40	5	x	x	Influenza	38	14	27	17
						y	y	Hyperthyroidism				
31-40	104	78	32	46	11	w	w	Pneumonia	67	13	22	32
						x	x	Pneumonia				
						y	y	Pneumonia				
						z	z	Nephritis				
41-50	128	96	48	48	11	v	v	?	85	35	34	16
						w	w	Pneumonia				
						x	x	Cancer				
						y	y	Cerebral hemorrhage				
						z	z	Cancer of stomach				
51-60	115	90	57	33	24	s	s	?	66	30	22	14
						t	t	Cancer of stomach				
						u	u	?				
						v	v	Pneumonia				
						w	w	Cancer				
						x	x	Peritonitis				
						y	y	?				
						z	z	Pneumonia				
61-70	65	47	36	11	18	u	u	Cancer of tongue	29	13	6	10
						v	v	Cancer of rectum				
						w	w	?				
						x	x	Cancer				
						y	y	Cancer				
						z	z	Apoplexy				
71-80	10	7	6	1	3	x	x	Pneumonia	4	1	0	3
	550	404	212	192	76				328	112	118	98

48 cardiac deaths, 11.8 per cent.

TABLE 9.—Mortality in T Wave Negativity, Notched Complexes

T Wave Negativity	Total	Patients Heard From	Males	Females	Cardiac Deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac Complaints
Derivation 1	34	28	23	5	15	53.6	11	1	8	2	0
Derivation 2	0	0	0	0	0	0.0	0	0	0	0	0
Derivation 3	154	103	33	70	14	13.6	86	31	34	21	10
Derivations 1 and 2	11	10	4	6	6	60.0	4	1	3	0	0
Derivations 2 and 3	25	17	9	8	4	23.5	10	2	6	2	1
Derivations 1 and 3	0	0	0	0	0	0.0	0	0	0	0	0
Derivations 1, 2 and 3	8	4	2	2	3	75.0	0	0	0	0	0
Total	232	162	71	91	42	25.9	111	35	51	25	11

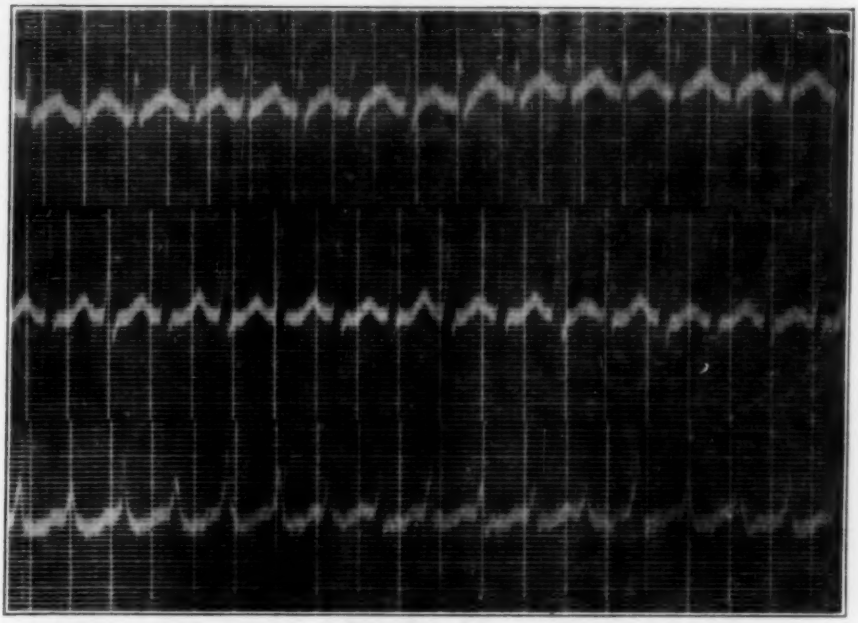

Fig. 8 (Case 252,579).—Notched Q R S, Derivation 3, showing progression. Aug. 15, 1919.

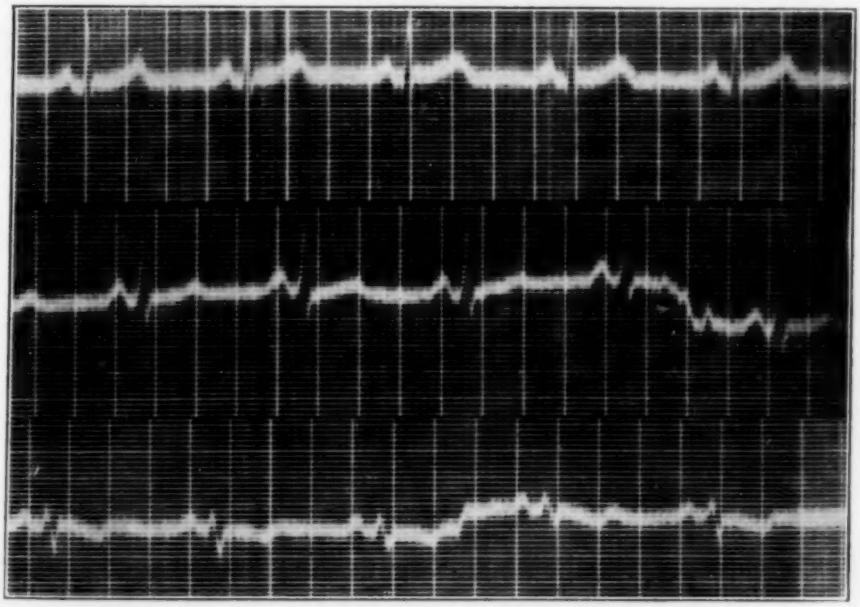

Fig. 9 (Case 252,579).—Notched Q R S, Derivation 3. Sinus rhythm. Aug. 18, 1919, just after tachycardia subsided.

TABLE 10.—Ventricular Preponderance in Slurred Complexes

Decade	Derivation 1			Derivation 2			Derivation 3		
	Left Preponderance	Right Preponderance	No Preponderance	Left Preponderance	Right Preponderance	No Preponderance	Left Preponderance	Right Preponderance	No Preponderance
1-10	0	1	1	0	0	0	0	0	0
11-20	0	4	1	0	0	0	2	0	0
21-30	2	10	6	2	0	0	3	5	2
31-40	3	6	8	2	2	1	12	5	15
41-50	6	6	4	4	0	6	6	1	6
51-60	5	1	0	9	0	1	16	1	9
61-70	1	1	1	6	0	2	6	1	4
71-80	0	0	0	1	0	0	0	0	0
Total	17	29	21	24	2	10	45	13	36

TABLE 11.—Etiologic Conditions in Slurred Complexes

		Degenerative Processes			Infections			Nutritional Disturbances			
	Total	Hypertension and Without Clinical Nephritis	Exophthalmic Goiter	Adenomas With Hyperthyroidism	Endocardial Valvular Disease	Chronic Myocarditis	Syphilis	Arteriosclerosis	Angina Pectoris (Patients with arteriosclerosis)	Congenital Heart Disease	Inconclusive Clinical Cardiac Findings
Derivation 1	67	5	9	2	28	6	2	4	3	1	10
Derivation 2	26	8	3	3	6	5	1	5	4	0	5
Derivation 3	94	22	13	2	10	8	4	7	3	1	27
Total	197	35	25	7	44	19	7	16	10	2	42
Percentage		17.8	12.7	3.5	22.3	9.6	3.5	8.1		1.0	21.3
		34.0			35.4						

TABLE 12.—T Wave Negativity in Slurred Complexes

Slurred Q R S	Total Slurred Q R S	T Derivation 1	T Derivation 2	T Derivation 3	T Derivations 1 and 2	T Derivations 2 and 3	T Derivations 1 and 3	T Derivations 1, 2 and 3
Derivation 1	67	4	0	12	0	6	0	0
Derivation 2	26	1	0	10	3	2	0	0
Derivation 3	94	3	0	20	0	7	0	4
Total	197	8	0	42	3	15	0	4
Percentage		10.8	0.0	56.8	4.0	20.3	0.0	5.4
		72 (39%)						

and auricular flutter, revealed a cardiac mortality of 11.8 per cent. This difference in mortality is certainly definite.

Two hundred ninety-seven patients are alive; ninety-four report their conditions as being worse, 131 as improved, and seventy-two as unchanged. Thirty-nine report no cardiac complaints. Tables 4 to 8 summarize these findings.

TABLE 13.—MORTALITY IN SLURRED COMPLEXES, DERIVATION 1

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1-10	2	2	1	1	1	.....	1	1	0	0	0
11-20	5	5	3	2	0	.....	5	1	1	3	1
21-30	18	14	6	8	3 x	x Influenza	11	4	5	2	1
31-40	17	14	5	9	5	.....	9	2	3	2	0
41-50	16	12	7	5	9	.....	3	0	3	0	0
51-60	6	6	5	1	3	.....	3	1	2	0	0
61-70	3	2	2	0	0	.....	2	1	0	1	0
Total	67	55	29	26	21	.....	34	10	14	8	2

20 cardiac deaths, 36.3 per cent.

TABLE 14.—MORTALITY IN SLURRED COMPLEXES, DERIVATION 2

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
21-30	2	2	0	2	0	.....	2	1	0	1	0
31-40	5	5	1	4	1	.....	4	0	1	3	1
41-50	10	8	4	4	1	.....	7	4	1	2	1
51-60	10	8	6	2	3 x	x Postoperative peritonitis	5	0	2	3	0
61-70	8	5	4	1	2	.....	3	2	0	1	0
71-80	1	0	0	0	0	.....	0	0	0	0	0
Total	36	28	15	13	7	.....	21	7	4	10	2

6 cardiac deaths, 21.4 per cent.

TABLE 15.—MORTALITY IN SLURRED COMPLEXES, DERIVATION 3

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
11-20	2	1	1	0	0	.....	1	0	0	1	0
21-30	10	9	3	6	0	.....	9	5	3	1	0
31-40	32	24	11	13	4 x	x Influenza	20	3	13	4	4
41-50	13	8	3	5	1	.....	7	2	3	2	2
51-60	26	17	11	6	5	.....	12	4	4	4	0
61-70	11	8	6	2	1	.....	7	1	3	3	1
Total	94	67	35	32	11	.....	56	15	26	15	7

10 cardiac deaths, 14.9 per cent.

TABLE 16.—Total Mortality in Slurred Complexes

	Total	Patients Heard From	Males	Females	Cardiac Deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac Symptoms
Derivation 1	67	55	29	26	20	36.4	34	10	16	8	[illegible]
Derivation 2	28	28	15	13	6	21.4	21	7	4	10	[illegible]
Derivation 3	94	67	35	32	10	14.9	56	15	26	15	7
Total	197	150	79	71	36	24.0	111	32	46	33	11

TABLE 17.—Control Series

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged
1-10	2	2	1	1	0	.....	2	0	2	0
11-20	7	6	4	2	1	.....	5	3	0	2
21-30	30	26	10	16	5 x	x Exophthalmic goiter; thyroidectomy	21	9	3	9
					y	y Pneumonia				
					z	z Exophthalmic goiter; hyperthyroidism				
31-40	54	44	14	30	7 w	w Pneumonia	37	16	14	7
					x	x ?				
					y	y Postoperative peritonitis				
					z	z Bronchopneumonia				
41-50	39	27	12	15	6 z	z Apoplexy	21	7	8	6
51-60	42	30	19	11	12 x	x ?	18	5	8	5
					y	y Peritonitis				
					z	z Cancer				
61-70	14	12	10	2	4 x	x Cancer	8	5	1	2
					y	y ?				
					z	z Cancer				
71-80	1	0	0	0	0	.....	0	0	0	0
Total	197	147	70	77	35	.....	112	45	36	31

21 cardiac deaths, 14.3 per cent.

TABLE 18.—Mortality in T Wave Negativity, Slurred Complexes

T Wave Negativity	Total	Patients Heard From	Males	Females	Cardiac Deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac Complaints
Derivation 1	8	6	5	1	3	60.0	3	2	1	0	0
Derivation 2	0	0	0	0	0	0.0	0	0	0	0	0
Derivation 3	42	32	10	22	5	15.6	27	4	17	6	3
Derivations 1 and 2	3	3	2	1	2	66.6	1	1	0	0	0
Derivations 2 and 3	15	15	6	9	4	28.6	11	3	4	4	1
Derivations 1 and 3	0	0	0	0	0	0.0	0	0	0	0	0
Derivations 1, 2 and 3	4	4	4	0	3	75.0	1	1	0	0	0
Total	72	60	27	33	17	28.3	43	11	22	10	4

In a previous article I emphasized the significance of the negative T wave in Derivation 1 alone as indicative of myocardial damage. More than one half (53.6 per cent.) of the patients with a negative T wave in this group have died of heart disease. Table 9 summarizes the T wave negativity. This observation demands careful investigation.

Slurred Q R S Complexes. — This group comprises those Q R S complexes in which localized thickening or slurring of the ascending or descending limb, or both, occurred. These changes are only slight departures from the normal.

Sixty-seven cases (34 per cent.) occurred in Derivation 1, thirty-six (18.3 per cent.) in Derivation 2, and ninety-four (47.7 per cent.) in Derivation 3. Like the cases with notched complexes, the majority (43.6 per cent.) were associated with preponderance of the left ventricle (Table 10).

Degenerative processes (34 per cent.) and infections (35.4 per cent.) occurred equally as causative disorders (Table 11).

The number of cases in which the clinical findings did not corrobate the electrocardiograms was proportionately greater than in the preceding group (forty-two cases, 21.3 per cent.).

About one-third (37.6 per cent.) of the cases were associated with negativity of the T wave, again largely affecting Derivation 3 (56.8 per cent.). Table 12 illustrates these changes.

Only sixteen cases (8.1 per cent.) of auricular fibrillation and six cases of delayed auriculoventricular conduction were recorded. Information has been received concerning 150 patients; thirty-six (24 per cent.) have died from heart disease. The control series revealed a cardiac mortality of 14.3 per cent. (Tables 13 to 17). A definite difference in mortality is again observed. One hundred eleven patients are alive, thirty-two are in worse condition, forty-six are improved, and thirty-three are unchanged. Eleven patients report no cardiac complaints. Table 18 summarizes T wave mortality.

DISCUSSION

Notching and slurring of the Q R S complex, occurring in isolated derivations of the electrocardiogram, suggests a local rather than a diffuse disorder of the ventricles. Whether or not this disorder is structural cannot be stated definitely at present owing to the meagerness of necropsy material. The fact that the notched complexes in isolated derivations are identical in contour with those in the cases with involvement of all three derivations makes actual changes in the myocardium a strong possibility.

The slurred complexes are graphically less conclusive, yet they are quite sharply contrasted with the normal. Figures 7, 8 and 9 illustrate progression from slurring to notching and from slight to marked notching.

I mentioned previously that a group of cases occurred in which the clinical findings were not sufficient to identify organic heart disease, but in which the electrocardiograms definitely depicted notching or slurring of the Q R S complex (16.5 per cent. of the total series). I do not believe that organic disease can definitely be excluded in this group. The majority of all the patients (82.5 per cent.) had fairly good "compensation" at the time of examination, that is, they were able to be up and about with relative comfort, and no instance of general anasarca was noted. The degree of "decompensation" was recorded as 0 to 2 (on a scale of 1 to 4, minimum to maximum), while in the minority group (17.5 per cent.) the grades were 3 to 4. This method of grading myocardial efficiency is, of course, inaccurate, but it permits comparative study. We are, therefore, dealing with a group of patients, whose myocardiums are quite efficient at the time of examination, and it seems possible that muscle changes, especially local disease, can be present before the grosser subjective and objective findings of myocardial disintegration become obvious.

That progression does occur is seen in the electrocardiograms of Case 252,579 (Figs. 7, 8 and 9), and in the mortality statistics where the percentage in both the notched and slurred complexes nearly double those of the control series.

CONCLUSIONS

1. Notching and slurring of the Q R S complex in isolated derivations of the electrocardiogram must be considered as graphic entities.

2. These changes probably indicate local disorders of the ventricular myocardium affecting the conduction system.

3. Etiologic disorders occurring in order of frequency were: (1) degenerative processes; (2) infections, (3) local nutritional disturbances, and (4) congenital heart disease.

4. The cardiac mortality in both the notched and slurred complexes practically doubled that of the control series.

THE INFLUENCE OF THE EXPOSURE TO THE ROENTGEN RAY ON THE PROGRESS OF TUBERCULOSIS *

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It is generally agreed that the best method for diagnosing tuberculosis of the genito-urinary tract is by the inoculation of the urine of suspected cases into the peritoneal cavity of a guinea-pig. However, this test loses much of its practical value because of the time which must elapse before lesions are apparent in the guinea-pig after inoculation. This work has been undertaken with two purposes in view; first, to shorten the time of development of tuberculosis in guinea-pigs, so that inoculation tests will be of more practical value to the clinician; second, to determine the rôle of lymphocytes as a factor in the protection of guinea-pigs against tuberculous infection. The exposure of guinea-pigs to the roentgen ray was suggested by the favorable report of John H. Morton,[1] in which it is stated that, whereas with ordinary technic a period of five weeks elapses before death, with the roentgen ray exposure tubercles are apparent in ten days. Fortunately, the guinea-pig is able to withstand massive roentgen-ray treatments without apparent injury to the general system. In Morton's experiments, the animals were roentgenized for ten minutes with the Coolidge tube, with the target twelve inches from the base of the container. Five milliamperes with an eight and one-half inch spark gap was used. From 1 to 2 c.c. of tuberculous urine was injected intraperitoneally.

The effect of the roentgen ray on the resistance of animals to infection has been a subject of discussion for several years. Simonds and Jones,[2] who were early workers in this field, concluded that mice and guinea-pigs exposed to the roentgen ray showed a greater resistance to infection than did normal animals. Lawen [3] found that the resistance to infection of strongly roentgenized rabbits was greatly reduced; also if the roentgen ray had not been applied for too long a time, the injection of bacteria was followed by a rise in the number of leukocytes, but with heavy doses of the roentgen ray, the injection was followed by a fall in the number of leukocytes. The cholera vibrio and typhoid

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1. Morton, J. H.: J. Exper. M. **24**:419, 1916.
2. Simonds, J. P., and Jones, H. M.: J. Med. Res. **33**:183, 1915.
3. Lawen, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:141, 1909.

bacillus were used in this experiment. Murphy and Ellis,[4] experimenting with mice, found that roentgenized animals died in the shortest time after inoculation with virulent organisms; next in order were splenectomized mice inoculated shortly after splenectomy; next were splenectomized mice inoculated eight days after splenectomy; animals inoculated eight days after splenectomy showed the same resistance as did normal animals. The most resistant animals were mice inoculated three weeks after splenectomy. Taylor and Murphy[5] report a series of experiments in which the progress of infection varied directly with the fluctuation of the lymphocyte count. A lymphocytosis was produced in mice by the transplantation of mouse cancer. Three mg. of a culture of bovine tubercle bacilli was injected intraperitoneally. The cancer immune mice died in 47.7 days, while the controls died in 20.3 days. Also, a series of mice were immunized against mouse carcinoma and roentgenized daily for seven exposures. The roentgenized mice lived 14.5 days following inoculation with tubercle bacilli. The controls lived 32.5 days.

Simonds and Jones[2] found that rabbits exposed to the roentgen ray for from ten to fifteen minutes a day for three weeks, showed a steady decline in the number of leukocytes, mostly of the lymphocytes. The formation of agglutinins was appreciably lowered.

Pappenheimer[6] determined the effect of the roentgen ray on the lymphocyte by using trypan blue, which is a specific stain for degenerating and dead cells. Rats were exposed to the roentgen ray for fifteen minutes, killed, and exsanguinated, and the lymphocytes obtained from the thymus gland. The cells showed 23.5 per cent. stained as compared with 10 per cent. stained in the control.

Hektoen[7] exposed white rats to the roentgen ray sufficiently long to produce a leukopenia lasting from fifteen to twenty days, continuing the exposures after the injection of sheep's blood, and found that lysin formation was markedly inhibited. He regards these results as an indication that antibodies are produced in the spleen, lymphatic tissue and bone marrow, as these are the structures which suffer from exposure to the roentgen ray. A specific example would be the formation by the lympocytes of antibodies against tuberculosis.

Against the favorable reports to which reference has been made is the work of Corper.[8] Following the technic of Morton, but using a culture of human tubercle bacilli instead of tuberculous urine, he found a slight involvement of the spleen and lymph nodes after thirty-

4. Murphy, J. B., and Ellis, A. W.: J. Exper. M. **20**:397, 1914.
5. Taylor, H. D., and Murphy, J. B.: J. Exper. M. **25**:609, 1917.
6. Pappenheimer, A. M.: J. Exper. M. **25**:633, 1917.
7. Hektoen, L.: J. Infect. Dis. **17**:415, 1915.
8. Corper, H. J.: Am. Rev. Tuberc. **2**:587 (Dec.) 1918.

one days, and a general tuberculosis after forty-eight days. He repeated the experiment, using, after the first roentgen-ray exposure, eight subsequent exposures, of five minutes duration, without shortening the time of death. The average white cell count was 2,500 per c.mm., as compared with 12,000 per c.mm. in the controls. Corper also used benzene injections, benzene inhalations, thorium X, Koch's old tuberculin, and ether, without increasing the susceptibility of the guinea-pig to tuberculosis. The effects of the roentgen-ray on the progress of tuberculous infection is yet an unsettled question, although it is an accepted fact that the white cells, and especially the lymphocytes, are markedly reduced by exposure to the roentgen ray. John Mackenzie [9] states that "it has been shown that if lymphocytes of the body are destroyed by roentgen radiation of an infected animal, the development of the infection is much more rapid." In view of the opposite conclusions arrived at by research workers, the subject is worthy of further investigation, not only for its immediate value to the clinician, but also for its bearing on the factors of immunity in tuberculosis.

In my experiments the method used by Morton has been followed, with certain variations. In all of the experiments, the inoculations were made intraperitoneally. The tubercle bacilli were grown on glycerin agar and Petroff's medium. The growth on the latter medium was the more luxuriant. The tubercle bacilli were weighed and then ground with fine sand in a mortar. All of the apparatus used was previously sterilized. The bacteria were suspended in a 0.7 per cent. sodium chlorid solution, and the proper volume of suspension injected.

In the first series, five guinea-pigs were exposed to the roentgen ray, using five milliamperes of current, an eight and one-half inch spark gap, with the target twelve inches from the base of the guinea-pig container. The Coolidge tube was used. The weight of these animals, as well as five controls, was recorded. On the following day, the roentgenized guinea-pigs and the controls were each injected with 1 mg. of a third generation culture of virulent human tubercle bacilli. White blood cell counts and differential counts were made on three of the roentgenized animals and three of the controls. These blood counts were repeated in ten days, and the weights were again recorded. One roentgenized guinea-pig showed a drop in the white cell count from 15,000 per c.mm. before exposure to 8,600 per c.mm. ten days after exposure. The least marked drop was from 14,000 to 10,400. One of the controls showed a drop from 12,000 to 11,400, while another showed an increase from 12,000 to 12,500. The results are recorded in the tables. A majority of the roentgenized guinea-pigs showed a

9. Mackenzie, J. J.: Oxford Med. **1**:276.

loss of weight after ten days, while the controls showed no appreciable difference. Two guinea-pigs of this series died on the twenty-first day, and the others of the series were killed on the same day. Three of the roentgenized and three of the control guinea-pigs showed tuberculous lesions, either grossly or microscopically.

TABLE 1—SERIES A. WHITE CELL COUNT

	Roentgenized			Controls		
	1	2	3	1	2	3
Before inoculation	15,800	16,500	14,000	16,000	12,000	12,200
Ten days after inoculation	8,000	9,000	10,400	15,000	11,400	12,500

TABLE 2.—SERIES A. EXAMINED TWENTY-ONE DAYS AFTER INOCULATION

	Roentgenized	Controls
1	Killed—necropsy negative	Microscopic lesions of liver and lymph glands
2	Killed—necropsy negative	Gross tubercles of spleen and glands. Rolled omentum
3	Microscopic lesions in lymph glands	Necropsy negative
4	Gross tubercles in spleen, liver and lymph glands. Rolled omentum	Necropsy negative
5	Caseous lymph glands and rolled omentum	Tubercles in spleen and lymph glands. Rolled omentum

TABLE 3.—SERIES A. VARIATION IN WEIGHT

	Roentgenized					Controls				
	1	2	3	4	5	1	2	3	4	5
Before inoculation	350	375	325	365	315	370	390	410	350	425
Ten days after inoculation	330	290	290	400	285	400	370	395	355	405

	Average Loss of Weight
Roentgenized guinea-pigs	43 gm.
Controls	4 gm.

In this series there was no difference observed in the development of tuberculous lesions in the roentgenized and control animals, but the roentgen ray was shown to have a marked effect on the white blood cells, especially the lymphocytes, and on the weight. There were two variations from the method used by Morton. The exposure to the roentgen ray was fifteen minutes instead of ten minutes, and a third generation culture of tubercle bacilli was used instead of tuberculous urine.

The above experiment was repeated, using the same culture, but exposing the guinea-pigs to the roentgen ray for ten minutes instead of fifteen minutes. The white blood cell count was not made in this series. Four roentgenized and four control guinea-pigs were inoculated after recording the weights. Two of the controls died on the third day from a generalized pyogenic infection. After ten days, there was no marked difference in loss of weight between the roentgenized and the control guinea-pigs. At the necropsy two of the roentgenized and one

of the control guinea-pigs showed tuberculous lesions. This indicated that there was no difference in the stage of tuberculosis between the roentgenized and the control guinea-pigs.

In the next group of guinea-pigs (Series C) the exposure to the roentgen ray was increased. Four animals were exposed for fifteen minutes, the first dose being given one day before, and the second dose six days after inoculation. One mg. of the culture used in series A and series B was injected. White blood cell counts made six days after the second exposure showed a drop from 13,600 to 2,200 cells per c.mm. in one animal, and from 14,300 to 2,800 in another.

TABLE 4.—Series B. Examined Twenty-One Days after Inoculation

	Roentgenized	Controls
1	Necropsy negative	Died on third day from pyogenic infection
2	Necropsy negative	Died on third day from pyogenic infection
3	Caseous lymph glands; rolled omentum....	Necropsy negative
4	Tubercles in spleen and lymph glands. Rolled omentum	Caseous lymph glands. Rolled omentum

TABLE 5.—Series B. Variation in Weight

	Roentgenized				Controls			
	1	2	3	4	1	2	3	4
Before inoculation	360	385	360	410	Died second day	Died second day	355	375
Ten days after inoculation	295	350	345	355			345	325

	Average Loss of Weight
Roentgenized guinea-pigs	43 gm.
Controls	40 gm.

TABLE 6.—Series C. White Cell Count

	Roentgenized			Controls		
	1	2	3	1	2	3
Before inoculation	13,600	15,200	14,300	10,200	12,800	16,000
Ten days after inoculation.....	2,200	5,600	2,800	12,400	11,000	15,400

The differential count showed practically all polymorphonuclear leukocytes, with 2 per cent. lymphocytes. The controls showed from 40 to 50 per cent. of lymphocytes. The blood smears, stained with Wright's stain, showed numerous fragments of basic staining material which I interpreted as being broken up white cells, since they were not present in the smears of blood from the control guinea-pigs. There was a consistent loss of weight observed which was not observed in the controls. One of the roentgenized guinea-pigs died on the twenty-fourth day, two guinea-pigs died on the twenty-sixth day, and one guinea-pig was killed on the twenty-eighth day. One of the controls died on the twenty-sixth day, one on the twenty-eighth day, and two were killed on the twenty-eighth day. Owing to an error, two of the

roentgenized guinea-pigs which died were not examined postmortem. The other two showed tuberculous lesions.

TABLE 7.—Series C. Variation in Weight

	Roentgenized				Controls			
	1	2	3	4	1	2	3	4
Before inoculation	390	415	295	345	325	370	325	320
Ten days after inoculation	340	360	310	340	335	356	335	295

	Average Loss of Weight
Roentgenized guinea-pigs	33 gm.
Controls	5 gm.

TABLE 8.—Series C. Progress of Infection

	Roentgenized	Controls
1	Killed on twenty-eighth day; necropsy negative	Killed on twenty-eighth day; necropsy negative
2	Died on twenty-fourth day; not examined postmortem	Died on twenty-sixth day; tubercles in spleen, liver and lymph glands
3	Died on twenty-sixth day; tubercles in spleen and lymph glands. Rolled omentum	Died on twenty-eighth day; tubercles in spleen and lymph glands. Rolled omentum
4	Died on twenty-sixth day; not examined postmorem	Killed on twenty-eighth day; caseous lymph glands; rolled omentum

Two roentgenized guinea-pigs were not examined owing to error.

Three of the controls showed tuberculous lesions and one control was negative. There was no appreciable difference in the time of death between the roentgenized and the control guinea-pigs.

Since there was a possibility that the roentgen-ray exposure which was given seven days after inoculation may have had a deleterious effect on the tubercle bacilli, the experiment as performed in series C was repeated, with the difference that two exposures were given with an interval of seven days, the inoculation being made one day after the second exposure. Two roentgenized and two control guinea-pigs were inoculated. One of the roentgenized animals died on the twenty-sixth day; the other one died on the twenty-ninth day. Postmortem examination revealed microscopic lesions in both animals. The controls died on the twenty-ninth and thirty-first day, respectively, both showing tuberculous lesions. In these experiments the animals were injected with a known tuberculous sputum.

Microscopic sections were made of the spleen, liver and mesenteric and inguinal lymph glands in those cases which showed no lesions microscopically. The sections were cut in celloidin and stained with hematoxylin and eosin. In only two cases not showing tuberculosis macroscopically were the lesions revealed by the microscope. In two cases showing tubercles grossly, the kidneys and lungs were also examined microscopically, but neither organ showed tubercles. The inguinal and mesenteric lymph glands, and the omentum were most frequently involved, while the spleen and liver, respectively, were next in the

order of frequency of involvement. The tubercles in the liver and spleen of animals not roentgenized showed large mononuclear and epithelioid cells around a necrotic center, with lymphocytes diffusely arranged peripherally. The blood vessels near the tubercles contained more than the ordinary number of polymorphonuclear leukocytes and lymphocytes, and there were a large number of these cells just outside of the blood vessels in the liver. This would seemingly indicate that the cellular elements of the tubercle are of hematogenous origin. The microscopic sections of tuberculous guinea-pigs which were roentgenized showed fewer polymorphonuclear leukocytes and lymphocytes than occurred in the controls.

Do the cellular elements of the tubercle originate from the blood or from the local tissue? Metchnikoff maintained that the tubercle is of leukocytic origin, and supposed that the giant cell and epithelioid cells are derived from the lymphocyte. This is in line with his general theory of the rôle of leukocytes. Baumgarten stated that the proliferative processes from local tissue are concerned with the function of the tubercle, basing his conclusion on the observation of mitotic figures in the local cells. Evans, Bowman and Winternitz [10] performed an ingenious experiment to determine the origin of the tubercle cells. They injected tubercle bacilli into the mesenteric vein of a rabbit, and then injected trypan blue into a vein. The stain showed a degeneration of hepatic endothelium, which seemed to indicate that the large mononuclear cells at the site of the tubercle are derived from fixed tissue and not from the lymphocytes.

The knowledge of the function of the lymphocyte is very indefinite. Because of the variation in classification of leukocytes it may be well to state that the term "lymphocyte" as used here includes only the small round cell leukocytes with a solid deep staining nucleus occupying most of the cell. Formerly, it was generally supposed that tuberculosis is always accompanied by a leukocytosis, and this was used as a differentiating point between typhoid fever and miliary tuberculosis. It has been observed, that with a mild tuberculous infection there is a relative lymphocytosis, but in some cases of visceral and pulmonary tuberculosis, the process is accompanied by a lymphopenia.[11] Warthin,[12] in 1896, reported two cases of tuberculosis with a marked leukopenia, in which the diagnosis was proved at necropsy. In one case, the white cell count was as low as 1,250 during the course of the disease. The differential count showed 5 per cent. of lymphocytes.

10. Evans, Bowman and Winternitz: J. Exper. M. **19**:283, 1914.
11. Gruner, O C.: Biol. Blood Cells, 1914.
12. Warthin, A. S.: Med. News **68**:89, 1896.

SUMMARY

I have attempted to hasten the progress of infection in guinea-pigs following tuberculous inoculation by exposing the animals to massive doses of the roentgen ray. In the first and second series of guinea-pigs there was no apparent difference in time of appearance of the tuberculous lesions in the roentgenized animals and the controls. In the third series, there was a difference of a few days in the time of death, the average time of death occurring two days earlier in the roentgenized animals than in the controls. This series received two roentgen-ray exposures. The fourth series showed the same difference in time of death between the roentgenized and the control animals, as was observed in Series C.

The exposure to the roentgen ray has had an appreciable effect on the body metabolism. It is possible that the more noticeable decrease in weight is due to the more rapid progress of tuberculosis, but post-mortem examination of the roentgenized and the control animals does not indicate this to be the fact.

The exposure to the roentgen ray has a profound effect on the leukocytes, especially the lymphocytes. A consistent drop in the white cell count and relative number of lymphocytes has been noted, the decrease being more marked in those animals subjected to more intense roentgenization. The microscopic sections of tuberculous liver tissue in the roentgenized guinea-pigs show fewer polymorphonuclear leukocytes and lymphocytes in the blood vessels than occurred in the controls, which effect is probably due to the roentgen ray.

The tuberculous lesions differ from the lesions in the controls in that they have very few lymphocytes in the outer zone. The epithelioid cells and large mononuclear leukocytes apparently are not decreased in number. There was nothing in the gross or microscopic appearance of the lesions to indicate that the tubercles in the roentgenized animals were further advanced than those in the controls. An inconsistency is noted in the frequency of tubercle formation in the spleen and lymph glands, as the lymphocytes are formed in the lymphoid follicles of the spleen and lymph nodes.[11] One would not expect these organs to be affected as readily as others if the lymphocytes are the main factor in combating tuberculosis.

CONCLUSIONS

1. *Effect of the Roentgen Ray on the Life of the Guinea-Pig.*—I have been unable to hasten the progress of the tuberculosis appreciably by exposure of the guinea-pig to massive doses of the roentgen ray.

2. *Effect on the Leukocytes.*—The leukocytes of the blood stream are markedly reduced in number by exposure to the roentgen ray. The

reduction is proportionate to the length of exposure with a given current and voltage. The lymphocytes are most markedly affected.

3. *Origin of the Tubercle Cells.*—The cells of the tubercle are probably derived both from the local tissue and from the blood. The presence of the usual number of epithelioid and large mononuclear cells in the tuberculous lesions of roentgenized guinea-pigs, where there is a marked diminution in lymphocytes, indicates that these cells are not of lymphocytic origin. The presence of an excess of lymphocytes in and around the blood vessels near the tubercles in nonroentgenized animals indicates that cells are carried to the lesions by the blood stream.

BOOK REVIEW

EXPERIMENTAL PHARMACOLOGY. By Hugh McGuigan, Ph.D., M.D., Professor of Pharmacology in the University of Illinois, College of Medicine. Philadelphia and New York: Lea & Febiger, 1919.

In his preface the author states that an attempt has been made to present experimental pharmacology in a brief, concise form, yet to give the student an adequate view of the field. The introduction and first chapter deal with general considerations of drug action, modes of drug administration and operative and other technical details. The succeeding chapters are devoted to the pharmacology of the various systems of the body, with selected experiments illustrating the action of drugs on these systems. Methods of biological standardization are described for those drugs for which these methods are commonly applied. The book is illustrated with a number of photographs, drawings and diagrams.

One criticism that might be offered is that the book contains too much extraneous matter. Thus the introductory chapters contain definitions and general statements that properly belong in a textbook of pharmacology. There is a detailed account of various methods of artificial respiration and resuscitation which seems quite out of place. There is also a considerable space devoted to statements of physiological and pharmacological facts with no accompanying demonstrative experiments.

The book should be favorably received by those teachers of pharmacology who desire to give a comprehensive laboratory course in the subject, as they will find a very large number of experiments from which to select the ones they especially desire.

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